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THE ABSENCE OF CONSPICUOUS INCREMENTS OF VENOUS PRESSURE AFTER SEVERE DAMAGE TO THE RIGHT VENTRICLE OF THE DOG, WITH A DISCUSSION OF THE RELATION BETWEEN CLINICAL CONGESTIVE FAILURE AND HEART DISEASE

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PERIPHERAL venous congestion is often interpreted by clinicians as indicating disproportionate failure of the right ventricle.[1, 2] Doubt of the validity of this interpretation[3, 4] stimulated us to attempt direct experiments on dogs. The controversy between those who believe that one side of the heart can fail while the other remains relatively competent and those who can conceive only of failure of the whole heart has been recently reviewed by Luisada.[5] In the experimental attack on this problem, interest has centered in the production of pulmonary edema by damaging the left side of the heart.[5] Therefore, although the right side of the heart has been damaged by ligation of the right coronary artery[6] or the injection of silver nitrate into the right ventricular wall,[7, 8, 9] these experiments were designed as controls, and the facts which chiefly interested us were not recorded.

Therefore, in acute experiments, we damaged the exposed right ventricular wall with a cautery, and, in chronic experiments, ligated the vessels supplying this wall, closed the incision, and studied the animals until death or recovery ensued. Only minimal changes of venous pressure followed the most extensive damage to the right side of the heart that we knew how to inflict. With the results of these experiments before us, we have reconsidered the dynamics of clinical congestive failure and discussed its relationship to weakness of the heart.

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ACUTE EXPERIMENTS

Dogs were anesthetized with 1 c.c. per kilogram of a solution containing 3 per cent morphine, 4.2 per cent chloralose, and 50 per cent urethane, injected intraperitoneally, and were given ether during the operation, if necessary. Carotid and femoral venous cannulae were inserted; the former was connected to a mercury manometer, and the latter to a manometer and a reservoir of physiologic salt solution. Venous pressures were taken by filling the manometer a little above the venous pressure and allowing the saline to run into the vein until equilibrium was secured.

Fig. 1.—The heart of Dog 41 after the right ventricular wall had been attacked repeatedly with a cautery. The lesion had been cut through, to permit estimation of its depth, when this photograph was taken.

Under artificial respiration the sternum was split and the pericardium divided to expose the heart. After a control period, a red-hot soldering iron was laid repeatedly all over the surface of the right ventricle to destroy the muscular layers and interrupt the superficial blood vessels. Observations of arterial and venous pressure were taken while reheating the cautery, so that these estimations alternated with the infliction of more damage. Soon the right ventricle ballooned out at each systole. When rupture threatened, usually when leakage actually began, the experiment was terminated by stopping the respiration pump. After death the heart was removed, and the right coronary artery cannulated at its mouth and injected with hot, colored gelatin. After

examination and description of the heart, pieces were taken for sectioning, and the rest preserved in formalin.

The results are recorded in Table I; the venous pressure was measured from an imaginary horizontal line halfway between the anterior and posterior aspects of the chest. The most extensive damage to the right ventricle was followed by an increase in venous pressure of a little less than 2 cm. H_2O in one experiment, about 1 cm. in two experiments, and by no significant change in the other. However, after the pump was stopped, the asphyxial response caused a high rise of venous pressure in each animal.

Post-mortem examination showed that the largest part of the right ventricular wall was destroyed completely and most of the remainder could not be injected, presumably because the supplying vessels had been interrupted, but small areas of the right ventricular surface usually escaped the cautery. The post-mortem findings in Dog 41 were fairly typical of all, and this heart is shown in Fig. 1. Gross examination showed that over two-thirds of the right ventricular pericardial surface was charred. Viewed from within, the endocardium under this area showed gray areas and hemorrhagic spots. Cuts through the lesion showed that the tissue which retained its normal color was less than 2 mm. thick in many places. A strip of right ventricle wall on the right margin, about one-fifth of the total ventricular surface, was not reached by the cautery. This area appeared normal, and blood vessels here were injected, but no other injected vessels were found in any part of the right ventricular wall. The left ventricle was normal. Examination of microscopic sections confirmed the gross impression. At least three-fourths of the right ventricular wall must have been functionless at the end of the experiment.

Evidently, therefore, destruction of a large part of the right ventricular wall was followed by little or no increase in venous pressure in our experiments; certainly nothing comparable to that seen in human heart failure was observed. However, the direct transference of our results to heart failure in man would be open to criticism. Since, with the chest open, venous pressure and venous return are not under their normal influences, our dogs might have failed to show a more conspicuous elevation of venous pressure because they were unable to do so, i.e., because the mechanisms needed had been destroyed by the anesthetic or the operative procedure. This very proper objection can be answered in part. When the animals were asphyxiated by stopping the pump, the venous pressure reached 14 to 18 cm. H_2O—levels equal to, or only slightly below, those found in many cases of human heart failure. Therefore, our dogs did not fail to increase venous pressure merely because the open chest or the operative procedure made a larger increase impossible. Nevertheless, the mechanism might be different in the two situations, so we sought further assurance in chronic experiments on unanesthetized animals with the chest closed.

TABLE I

ACUTE DAMAGE TO THE RIGHT VENTRICLE OF ANESTHETIZED DOGS, WITH CHEST OPEN AND ARTIFICIAL RESPIRATION

TIME	MEAN B. P. (MM. HG)	VENOUS PRESSURE (CM. H_2O)	EXP. DOG 40 7.2 KG.
3.34	110	6.3	
3.45	120	6.5	
3.52	126	6.3	
3.58	132	6.5	
4.07	126	5.9	
4.10			Damage to R. V. begun
4.11	134	6.0	
4.15	116	5.7	
4.20	104	5.9	
4.24	90	6.1	
4.31	90	5.8	
4.36	86	5.8	
4.45	74	6.7	
4.51	64	6.4	
4.58	66	7.1	
5.06	70	7.9	
5.12	74	8.3	
5.16	70	8.1	
5.22		18.0	Art. resp. off

TIME	MEAN B. P. (MM. HG)	VENOUS PRESSURE (CM. H_2O)	EXP. DOG 41 13 KG.
2.36	114	8.0	
2.37	114	8.5	
2.41	114	7.9	
2.42	114	8.3	
2.46	124	7.9	
2.49	126	7.6	
2.53	130	7.8	
2.54			Damage to R. V. begun
2.56	120	7.8	
3.00	120	7.8	
3.10	118	7.4	
3.24	130	8.0	
3.29	124	8.3	
3.34	124	9.0	
3.37	120	9.0	
3.50	120	8.3	R. V. perforated
			Art. resp. off
3.55		14.0	

			EXP. DOG 42 9.3 KG.
3.02	68	6.6	
3.11	76	6.8	
3.12			Damage to R. V. begun
3.14	74	6.8	
3.19	84	6.3	
3.28	90	6.5	
3.39	88	6.2	
3.46	90	6.5	
3.54	92	6.5	
3.58	92	6.5	
3.59	148	15.0	Art. resp. off

			EXP. DOG 44 9.5 KG.
2.55	130	7.8	
3.01	134	7.8	
3.04	134	8.0	
3.07	136	8.0	
3.08			Damage to R. V. begun
3.11	128	8.6	
3.15	112	8.7	
3.19	94	8.6	
3.27	76	8.3	
3.28	170	16.0	Art. resp. off

CHRONIC EXPERIMENTS

Hill, Johnston, and Wilson,[6] reporting late electrocardiographic effects after ligation of the right coronary artery, had demonstrated that dogs could survive this damage to the right side of the heart for long periods. These authors were interested in the electrocardiographic changes, and venous pressure was not measured. Communication with Dr. Wilson disclosed that no venous congestion had been observed; and we had no doubt that, if conspicuous venous congestion had occurred, it would have been both noted and reported. Nevertheless, it seemed wise to repeat this type of experiment, and make careful measurements of venous pressure.

After appropriate anesthesia, and with a sterile technique, the visible branches of the right coronary artery, descending on the surface of the right ventricle, were ligated, and the animals allowed to recover. Several dogs did not survive the operation; one lived thirty-six hours, and one recovered completely and was sacrificed after three months. In the two survivors, venous pressure was estimated by training the dog to lie quietly on its back and measuring the height of the column of blood distending the large superficial vein on the interior aspect of the hind leg. When the skin was shaved, this could easily be seen, and the vein could be filled and emptied by raising or lowering the limb, much as the veins on the back of the hand are studied in man.

TABLE II

VENOUS AND ARTERIAL PRESSURES IN DOGS WITH INFARCTS OF THE RIGHT VENTRICULAR WALL

DATE	VENOUS PRESSURE (CM. H_2O)	REMARKS
3/24		Dog 378. Operation, all visible branches of the right coronary artery ligated
3/25	4.0	Dog weak
3/26		Dog found dead, necropsy lost by accident
2/20		Dog 539. 7.8 kg. Operation, several branches of right coronary ligated
2/27	5.5	Dog weak
3/6	4.0	Dog appears well and lively
3/13	3.0	Dog appears well and lively
3/20	5?	Dog has distemper but is lively
3/30	6.5	Dog has distemper but is lively
4/15	4.0	Slight nasal discharge persists
4/24	4.0	Appears well and lively
5/12	7.5	Appears well and lively
5/26	4.0	Appears well and lively
5/27		Dog sacrificed

The results are recorded in Table II. No substantial increases in venous pressure were found. Palpation for the liver and auscultation of the chest revealed nothing abnormal at any time.

We followed one dog for three months and then sacrificed it. A large infarct, roughly 3 by 4 cm., could be clearly identified in the surface of the right ventricle. No other cardiac lesions were found.*

DISCUSSION

It is well known that the right coronary artery may send branches to the left ventricle, and it is therefore entirely possible that, in tying or cauterizing vessels on the right ventricular surface, the blood supply to a portion of the left ventricle was interrupted. However, no lesion of the left ventricle was demonstrated at necropsy in any experiment. Also, if the right ventricle is weakened, and its output diminishes, the left side of the heart will not be as well filled, to the detriment of its function, even though its potential strength may be intact. But although we are prepared to admit that left ventricular function may

*Dr. W. E. Ehrich of the Pathology Department assisted in the necropsy.

have been impaired by our procedures, the total destruction of such a large part of the right ventricular wall, and its lack of function as judged by systolic bulging during life and our inability to inject the vessels after death, make it obvious that the right ventricle was disproportionately weak in relation to the left. Manifest systemic venous congestion and increased venous pressure have often been attributed to such a disproportion of cardiac strength, but in our hands the direct experiment failed to reproduce these effects.

In view of the negative character of our results and the absence of any mention of congestion in other experiments[6-9] in which the right ventricle was damaged, one wonders how the conception that venous congestion indicates right-sided heart failure originated. When asked this question, many intelligent clinicians of our acquaintance have supported their views by the dam and stream analogy, as have some leaders in this field.[10] They conceive of a stream with a dam, forming a mill pond, and of the heart as a pump to lift water over the dam. If such a pump weakened, obviously the water in the mill pond would rise.

This analogy is popular because, since it is within the experience of everyone, the facts are very easily grasped. But the difficulty should be apparent as soon as it is pointed out; in the example cited there is no circulation. To make this analogy closer, although it would still be very imperfect, one might conceive of the pump drawing water from the pond, but also pumping this water back into the pond again, its only source of supply. One easily sees that under these circumstances the rate of pumping has no relation to the level of water in the pond.

But two other arguments cannot be dismissed so lightly. In our circulation schema,[3] when the left "heart" was weakened, "blood" was transferred from the systemic to the pulmonary circuit, and, when the right "heart" weakened, from the pulmonary to the systemic. One would certainly expect similar mechanical effects to take place in the body when one side of the heart weakened. But while it is easy to think of blood drawn from the systemic circuit flooding the lungs in left-sided heart failure, one wonders whether blood spared from the lungs could possibly produce the massive venous and hepatic congestion we so often see in the clinic. Indeed, more blood than the normal lungs are believed to contain has often been transfused into the systemic veins without reproducing a noteworthy degree of venous congestion. Therefore, although we concede that right-sided heart failure may be a factor in clinical systemic venous congestion, the evidence indicates that it plays only a minor part. It is to be noted that the venous pressure did rise a little in some of our acute experiments, especially in Dog 40, in which the arterial blood pressure was maintained. Transference of blood from the lungs was doubtless a factor in this effect.

Another mechanical effect which increases the amount of "blood" in the "veins" can be easily demonstrated in any circulation schema with a pump, valves, elastic tubes, and a peripheral resistance. In such

a system, as "cardiac output" diminishes, "arterial" pressure falls and "venous" pressure rises as "blood" is transferred from the "arterial" to the "venous" side. In our animals this process may well have been a factor in the small increments of venous pressure which, late in the experiments, accompanied a diminishing arterial blood pressure. But physiologists who are inclined to give great weight to this analogy do not, perhaps, realize that manifest venous congestion is not regularly found in moribund states, although the arterial pressure falls and the circulation must always diminish before it comes to rest. Therefore, one must conclude either that this mechanism is not of sufficient importance to produce manifest congestion of veins of patients, or that its effect is regularly overcome by another mechanism, such as a general relaxation of peripheral vessel tone, which must be assumed to occur as death approaches, and to be absent in congestive heart failure. Regarded in either way, it is evident that this mechanical effect of a diminished circulation is of less importance than other mechanisms which may influence venous pressure.

But if the massive venous congestion which we so often see in the clinic is not due to predominantly right-sided heart failure or to diminished cardiac output,[1, 11] to what should it be attributed? Clinicians have been slow to realize the multiplicity of noncardiac factors which might cause venous congestion and increased venous pressure. On the other hand, physiologists have suffered from the lack of a clear conception of certain facts about congestive failure as we see it in the clinic. Three such facts which bear on any theory of congestive failure may now be reviewed.

First, the venous congestion of cardiac patients persists in large measure after the heart has ceased to beat.[4] After death, the average pressure in the veins of cardiac patients who died with venous congestion exceeds that of patients who died without heart disease by an amount approximately equal to the difference present during the last illnesses. This fact surely indicates that any connection between venous congestion and cardiac function must be indirect, for the abnormality persists after cardiac function has ceased.

Second, bimanual pressure with one hand above, and one below, the right upper quadrant will distend the neck veins of many patients with heart disease; this maneuver has been used as a test for incipient congestive failure in Europe. In such patients the difference between the congestion during this pressure and its disappearance when pressure is released is surely not due to any change in the potential strength of the heart. It is obvious, therefore, that changes in the peripheral circulation are able to determine the presence or absence of venous congestion in these cases.

Third, the diuresis caused by mercurial diuretics often leads to rapid disappearance of the venous congestion. The disappearance of venous congestion which follows the administration of digitalis or the xanthines

may be attributed to improvement of the circulation from cardiac stimulation, but, when a similar effect follows the administration of a mercurial diuretic, this explanation is not valid, for mercury depresses the heart in any concentration that affects it at all.[12] Apparently, the common factor in the action of these three groups of drugs is their ability to eliminate fluid from the body; and the benefit which often follows a low salt diet[13] or the direct removal of fluid by tapping or Southey's tubes is additional evidence of the importance of this factor. Here we have evidence of another factor in the genesis of venous congestion which is only remotely, if at all, related to the heart.

With these facts in mind, let us attempt to assay the more important factors which might contribute to venous congestion in man. The first to consider is distention of the elastic vessels by the increased volume of blood which is so regularly found to accompany congestion of the veins in tests made during life.[14] Passive distention due to hypervolemia is a satisfactory explanation for the increased pressure throughout the vascular system, i.e., the increased static pressure which is found after death in cases in which there was venous congestion during life.[4] But unless the methods are playing us false, not all patients with hypervolemia, e.g., in polycythemia vera,[15] have venous and hepatic congestion. Therefore, the blood vessels must be assumed to play an active part in both the pressure and the distribution of blood within them.

That a widespread increase of vascular tone can raise venous pressure was first suggested to us by results in an animal experiment reported before,[16] in which, during the early part of the asphyxial response, cardiac output and arterial and venous pressure were increased at the same time. The asphyxial rise in venous pressure in the experiments reported in Table I of this paper was doubtless of this type, for the heart was observed to be beating with increased vigor when arterial and venous pressures were elevated. Such a generalized increase in intravascular pressure cannot be explained as the mechanical consequence of changes in cardiac activity and arteriolar resistance. Occurring far too rapidly to allow the assumption of an increase in blood volume with passive distention of vessels, a widespread increase in vascular tone, without compensatory relaxation elsewhere, is the explanation which naturally suggests itself. That a similar widespread increase in vascular tone might take place in man has been suggested.[17]

Pressure on blood vessels from without, as by fluid in the body cavities or when edema distends the skin, must be another factor, for this would produce much the same effect as active contraction of vessel walls. But since large hydrothoraces, acites, and the massive edema of nephrosis are often unaccompanied by venous congestion, this factor is probably a small one in most cases.

Nevertheless, a qualification must be made concerning the factors which we believe to be minor. In normal subjects many veins are partly collapsed, and the circulation obviously has an easily available

reserve capacity. It is under such conditions that transference of blood to the veins by the factors we have called minor causes little manifest congestion and little or no pressure changes; but if the vascular system were full and the veins already distended, the transference of small amounts of blood to the veins would have a much greater effect on the pressure within. Thus, it is only when it acts by itself that we expect cardiac weakness to cause no manifest venous congestion; surely, our hospitals are full of cases of angina pectoris without venous congestion. But if the blood volume was first increased, one would expect the minor factors to be more potent, so that the hearts' strength might be more accurately reflected by changes in venous pressure.

The direct experiments on dogs, the behavior of our circulation schema,[3] and the studies made on man[4] provide evidence against the commonly accepted doctrine of a direct mechanical relation between the heart and what is called congestive heart failure, but this evidence does not deny a relationship of another kind. The evidence for some kind of relationship is strong indeed; it consists of the impressive frequency of this complication late in the course of patients who have been long afflicted with chronic heart disease of many types. Other evidence, obtained in this laboratory,[18] supports this conception, for, using a physiologic measure of cardiac strength, namely, the ratio of the left ventricle's work per beat to the size of the heart, cardiac weakness was found to be characteristic of those patients who had passed through congestive failure, and so could be expected to suffer from it again. But in these data, also, there is evidence against a direct mechanical relationship, for no congestion was present when these tests were made, even though cardiac weakness was demonstrated. Nevertheless, it must be emphasized that this evidence and our failure to produce manifest congestion by directly damaging the heart does not refute the possibility of an indirect relationship, with time-consuming physiologic steps in between.

A plausible train of events relating the heart and venous congestion is suggested by McMichael's data:[19] The heart weakens and the circulation diminishes; as the bone marrow is stimulated by oxygen lack, the blood volume increases; the excess blood accumulates in the veins and congests them; and better cardiac filling from the increased venous pressure improves the cardiac output, so that normal circulation may be regained in some cases.

In the present state of our knowledge, other trains of events can also be conceived: The weakening heart could be thought of as diminishing renal circulation, for there is certainly good evidence of diminished kidney function in cardiac cases; specific renal insufficiency might cause the characteristic retention of fluid and electrolytes; this retained fluid increases blood volume and accumulates in tissues pressing on the patent vessels; to accommodate the excess, blood accumulates in the most distensible vessels, the veins, and also in the lungs, where it displaces some

of the air, and symptoms such as dyspnea result. Whether such fluid retention could explain the whole picture is debatable, but the prompt relief obtained by many patients when diuresis is established is most suggestive.

The similarity of the manifestations of overdosage with desoxycorticosterone[20] to those of congestive failure permits one to speculate about a train of events going through the endocrine system, and this does not exhaust the possibilities.

None of these speculations result in a perfectly satisfactory theory, for neither do the signs and symptoms of congestive failure regularly follow prolonged exposure to anoxemia at high altitudes, nor do all renal lesions which cause retention of water and electrolytes cause venous congestion. Knowledge about the action of desoxycorticosterone is still too scanty to permit an opinion of the closeness of the analogy. Indeed, although the old conceptions no longer satisfy us, we have nothing equally definite with which to replace them.

But one point must be strongly emphasized. As soon as one abandons the conception of a direct mechanical relationship between heart disease and congestive failure, and tries to substitute a train of events, one must concede that there may be other causes of congestive failure than heart disease. For example, if anoxemia of the bone marrow is a link in the chain, anoxemia from causes other than heart disease should cause congestive failure. If the chain goes by way of the kidney, renal lesions might cause it. It is sobering to reflect that, in many cases of congestive failure, heart disease was not the initial event; renal disease, as in the hypertensive cases, or pulmonary disease is often the initial event in the train. We have records of cases of this type in which the heart muscle at necropsy showed little or nothing to suggest that it was weak. One can contend that the pathologists' methods are inadequate, but it is becoming apparent that other explanations are possible.

The pathologist is unable to tell from post-mortem examination of the heart which patients have died in congestive failure. A heart muscle which appears grossly and microscopically normal at necropsy is often judged by clinicians to have been weak during life. It is our contention that the criterion for cardiac weakness that is usually employed, namely, the presence of venous congestion, is unsatisfactory. It is to be hoped that, as knowledge improves, the clinical and pathologic evidence of cardiac weakness will be brought closer together.

Knowledge of the dynamics of venous congestion in man is still far from complete; the point to be made here is that factors concerned with the volume of blood and the tone of the blood vessels seem most likely to be able to cause it, and that the mechanical factors directly connected with weakness of the right side of the heart, or of the whole heart, seem less important. This conclusion is supported by the results of our experiments.

CONCLUSION

By directly damaging the right ventricle of the dog's heart in acute and chronic experiments we failed to produce more than a minimal increase in peripheral venous pressure. Our results give no support to the view that the peripheral venous congestion and the large increment of venous pressure so often associated with cardiac disease in man are caused directly and predominantly by failure of the right ventricle.

The relation of cardiac disease to venous congestion in man is discussed.

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THE TETRALOGY OF FALLOT

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WE HAVE had the opportunity of studying, at necropsy, the organs of two patients, 53 and 43 years old, respectively, whose hearts showed the complex of lesions commonly described as the tetralogy of Fallot. These include pulmonic stenosis, defect of the interventricular septum, dextroposition of the aorta, and hypertrophy of the right ventricle. These cases are unusual in a number of respects, not the least of which was the long period of survival. Abbott[1] considered twenty-five years to be the maximum duration of life, although she listed certain cases in which the patient lived longer. As far as we have been able to ascertain, only one case has been reported in which the patient survived longer than the first of our two patients, namely, Paul White's noted musician.[3] It is apparent that the functional disturbances caused by the tetralogy are of a very serious nature, and are not consistent with life for more than a relatively short time. It is of great interest that in both of our cases there were factors which, although different in each, tended to alleviate the serious functional changes. These mitigating factors may explain, in part, the unusual longevity of both our patients.

REPORT OF CASES

CASE 1.—This patient was 53 years old at the time of his death. He was born in Czechoslovakia, and had lived in the United States for 35 years. He worked as a coal miner for many years, and as a laborer and building superintendent. No information is available concerning details associated with his birth. He recalled, however, having been warned during childhood "not to run too much" because he had a "bad heart." The patient stated that he had "always" experienced dyspnea on severe exertion, which had impeded, but did not prevent, arduous physical labor.

At the age of 37 years, sixteen years before death, the patient noted the onset of frequent attacks of fleeting migratory joint pains involving nearly all the joints of the body, and occasionally accompanied by fever. Eighteen months before death the patient was confined to bed for about two weeks because of dyspnea, orthopnea, and edema of the ankles. These symptoms disappeared with rest in bed alone. Eleven months before death the patient was admitted to another hospital because of dyspnea at rest, orthopnea, edema of the face and ankles, cough, bloodtinged sputum and frequency of urination. On admission there, his temperature was 98.6° F., his pulse rate, 76, his respiratory rate, 20, and his blood pressure, 140/70. The patient was "somewhat" cyanotic and the neck veins were dilated. A moderate number of medium moist râles were present at the bases of the lungs, together with some scattered dry râles. The point of maximal impulse of the heart was at the midclavicular line. There was an increase in dullness to the right of the sternum.

From the Department of Pathology, Welfare Hospital for Chronic Diseases, New York City. Case 1 is from the First Medical Division, Dr. Walter Lough, Director. Case 2 is from the Third Medical Division, Dr. J. Murray Steele, Director.
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Systolic and diastolic apical thrills were noted, and systolic and diastolic murmurs were present over the entire precordium; their maximal intensity was in the fifth intercostal space to the left of the sternum. The murmurs were thought by another observer to be loudest at the apex and transmitted to the left axilla. The edge of the liver was felt 2 cm. below the costal margin. The extremities showed "early clubbing" and "1 plus cyanosis." The electrocardiogram showed regular sinus rhythm, right axis deviation, a P-R interval of 0.20 to 0.24 second, and many junctional and ventricular premature contractions. A teleoroentgenogram showed enlargement of the heart to both sides. The urine was essentially normal. The hemoglobin was 98 per cent, with 4,800,000 erythrocytes. The total and differential leucocyte counts were normal. The blood Wassermann reaction was negative. A diagnosis of congenital heart disease, with interventricular septal defect, was made. The patient was treated with diet, limitation of fluid and salt intake, bed rest, sedatives, and digitalis. He improved rapidly and the diastolic thrill and murmur disappeared.

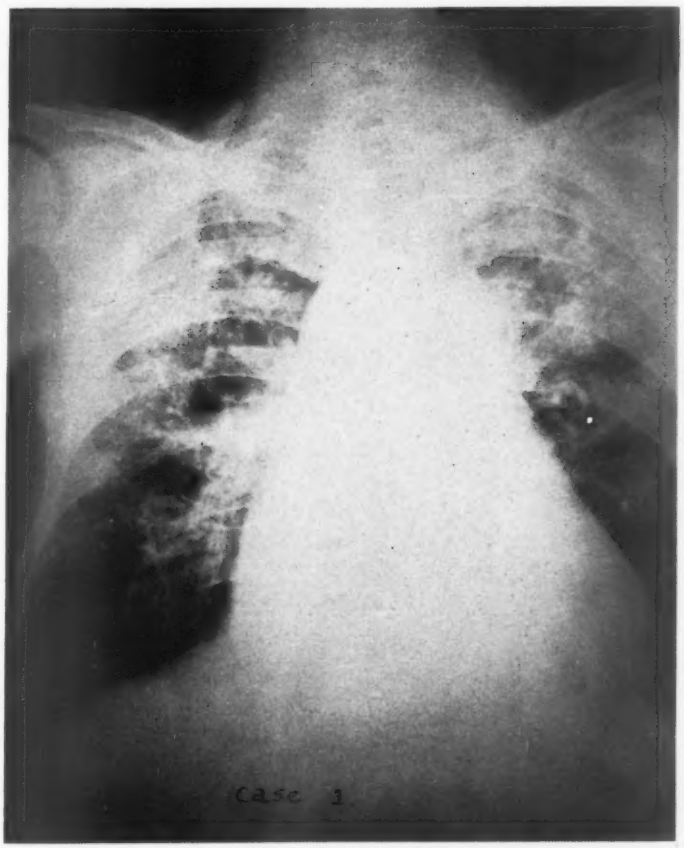

Fig. 1.—Case 1. Teleoroentgenogram, terminally.

Four months before death, auricular fibrillation was noted. Three months before death the patient was readmitted to the same hospital because of the reappearance of signs and symptoms of congestive failure. He had auricular fibrillation, with a ventricular rate of 76 and a blood pressure of 106/70. The physical signs were essentially the same as on the first admission, except that no diastolic thrill or

murmur was observed. Clubbing of fingers and toes with cyanosis of nail beds was present.

Fluoroscopic examination showed prominence of the pulmonary conus, dilatation of the pulmonary artery, enlargement of the inflow tract of the right ventricle, and lengthening and rounding of the left ventricle. Except for the presence of auricular fibrillation, the electrocardiogram was similar to that described above. The hemoglobin was 70 per cent and the erythrocyte count, 3,520,000. A diagnosis of rheumatic heart disease, with possible tricuspid insufficiency, was made. He improved only slightly with treatment.

Patient was transferred to Welfare Hospital two weeks before death. The physical signs were essentially the same. The cyanosis was thought to be mild; clubbing of the fingers was described. One observer believed that he could distinguish a diastolic thrill and murmur. Despite therapy, failure increased, and patient died of pulmonary edema twelve days after admission. The urine showed 1 plus albumin and an occasional leucocyte and hyaline cast. The hemoglobin was 82 per cent, with 4,020,000 erythrocytes. The total and differential leucocyte counts were normal. The urea nitrogen was 14.6 mg. per cent. Roentgenographic and electrocardiographic examination showed nothing new.

Autopsy was performed sixteen hours after death. There were definite clubbing of the fingers and toes, moderate edema of the lower extremities, and ascites (4,100 c.c.).

There was a chronic, progressive, tuberculous process in the upper lobes of both lungs, with fibrosis, caseation and cavitation, and bronchogenic spread to the right lower lobe.

The liver weighed 1,700 grams. The capsule and cut surface revealed fine nodules which averaged 3 mm. in diameter. The microscopic diagnosis was cardiac cirrhosis.

The spleen weighed 310 grams, and was intensely engorged. The pancreas was normal grossly, but, microscopically, revealed the atrophy of the peripheral portions of the lobules which is characteristic of long-standing congestion.

The heart weighed 970 grams; there were dilatation and hypertrophy of all four chambers, but both the hypertrophy and dilatation were more marked on the right. The pericardium was thickened, and the pericardial space was almost completely obliterated by thin, fibrous adhesions. No fresh fibrinous exudate was noted grossly. The myocardium of all four chambers, especially the right ventricle, was thickened. The right ventricular wall was 2.0 cm. thick at the base, 1.5 cm. midway to the apex, and 0.9 cm. at the apex. The left ventricular wall was 1.5 cm. thick at the base, 1.3 c.m. midway to the apex, and 1.1 cm. at the apex. Section of the muscle revealed no gross evidence of fibrosis or infarction. The endocardium showed small patches of thickening throughout. There was a defect, about 4 by 3 cm. in size, in the most basal portion of the interventricular septum. The aorta was so situated that approximately one-third of its lumen lay above the right ventricle and two-thirds above the left ventricle. The tricuspid ring was 13.5 cm. in circumference. The valve leaflets were thickened and deformed, with shortening, thickening, and fusion of the chordae tendineae. In one area, the fusion of the chordae tendineae had resulted in fenestration at the margin of one of the leaflets. The appearance suggested that stenosis (?) and insufficiency had been present. A thin sheet of tissue resembling normal valve leaflets (in contrast to the thickened leaflets which were actually present), with chordae tendineae at its edges, was found. It was attached superiorly to the base of the aorta, and ran transversely from one of the tricuspid leaflets, parallel with the septal defect. It may have, in part, occluded the opening in the septum, as well as blocked off the lumen of the aorta from the right ventricle. The pulmonic valve was bicuspid. The leaflets were very markedly thickened and sclerotic. The orifice was 5.5 cm. in circumference, and of narrow ellipsoid shape. Deep within both sinuses there were fibrotic nodules which appeared to be acquired, rather

than congenital lesions. The pulmonary conus was narrowed and hypoplastic, and the lower orifice (3.5 cm. below the valve edge) measured 7 cm. in circumference and was circular in shape. The wall of the conus was considerably thickened and opaque.

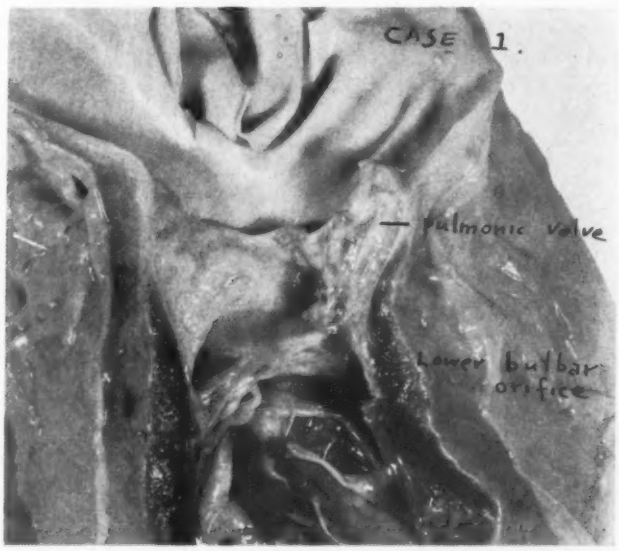

Fig. 2.—Case 1. Pulmonary conus.

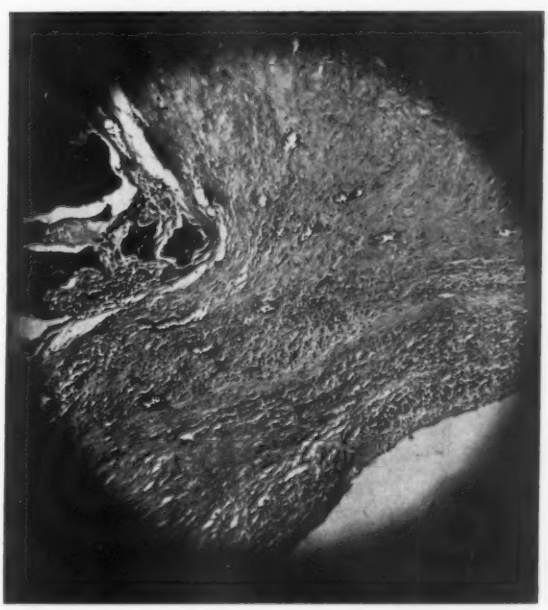

Fig. 3.—Case 1. Section of tricuspid valve.

The pulmonary artery was somewhat dilated. The mitral valve was thin and showed no gross fibrosis. The ring was 11 cm. in circumference. The aortic valve was likewise entirely normal. The aortic ring measured 9 cm. The coronary orifices were widely patent. The coronary arteries showed minimal atherosclerotic changes. Both the left descending and circumflex branches were larger than the right coronary.

The right coronary was particularly small, but its marginal branch was somewhat larger than would have been expected. No narrowing or occlusions were noted. The aorta showed a moderate degree of atherosclerosis. The measurements of the heart were made after fixation.

Microscopic Description of Heart.—The pericardium consisted of a very thick layer of fibrous and areolar tissue. It was very richly vascularized, and contained a great many small capillaries with swollen endothelial cells, and many larger congested vessels with thickened walls. In a few isolated areas there was a slight, diffuse lymphocytic accumulation. Some hyaline changes were noted in the pericardium over the auricles. Some of the muscle bundles of the myocardium were hypertrophied, and others were atrophied. There was a diffuse increase in interstitial fibrous tissue which, in some areas, was rather marked. Some increase of fibrous tissue immediately surrounding blood vessels was noted. In several areas there were perivascular accumulations of lymphocytes and monocytes, with fibrillation of collagen. No Aschoff bodies were seen. The endocardium was somewhat thickened, especially in the auricles. The wall of the pulmonary conus consisted of a very thick layer of fibrous connective tissue, part of which was hyalinized. In some portions of this tissue there was a moderate accumulation of mononuclear cells, apparently fibroblasts, lymphocytes, monocytes, and plasma cells. Many congested capillaries were present. Sections of the pulmonic valve revealed that it was considerably thickened and deformed. In some areas there was evidence of hyalinization, calcification, vascularization, and lymphocytic cellular infiltration. The elastic tissue stain revealed a loss of all organized elastic tissue throughout the valve, including the nodular structures at the base. A similar process was present in the tricuspid valve, where the cellular infiltration was perhaps more intense. The aortic valve showed some calcification, without vascularization or cellular infiltration. The mitral valve contained some calcific deposits at the base, but showed no cellular infiltration or vascularization.

CASE 2.—The patient was 43 years old at the time of death. She recalled having been told that at birth she had been a "blue baby." In childhood she would become dyspneic and cyanotic on moderate exertion. A history suggestive of rheumatic infection could not be elicited. At the age of 14 years, an operation was performed for Pott's disease. The patient was hospitalized for mild congestive failure at the age of 25 years, and repeatedly thereafter. Digitalization was started at the age of 34 years. When she was 41 years of age she had a cerebral accident which left her with left-sided hemiplegia.

At the age of 43 years, the patient was admitted to this hospital because of congestive failure. Physical examination revealed a chest deformity associated with kyphosis of the spine, resulting in an increase in the anteroposterior diameter. The degree of dilatation of the veins, pulmonary congestion, hepatic engorgement, and peripheral edema varied during her hospital stay. The heart was thought to be enlarged; the point of maximal impulse was felt at the fifth intercostal space just outside the midclavicular line. A diffuse systolic thrill was present over the entire precordium, but was most marked at the apex. A harsh, rough, loud murmur, extending through systole and most of diastole, was present over the whole precordium; it was maximal at the fourth intercostal space just to the left of the sternum. The rhythm was regular, and the rate averaged 86. The blood pressure ranged from 180/130 to 230/160. Cyanosis was not present except during attacks of failure.

Her course was characterized by attacks of transient coma, associated with vague neurologic changes and described as hypertensive encephalopathy and congestive failure of varying degree. The failure at first responded to digitalis and diuretics. The patient was discharged from the hospital two months before death, only to return, on the day prior to death, with coma and severe failure.

The hemoglobin was 98 per cent, the erythrocyte count, 4,950,000; the total and differential leucocyte counts were normal. The urine concentrated to 1.016 and contained 4 plus albumin. Terminally, occasional leucocytes, erythrocytes, and casts were noted. The urea clearance was 38 per cent of normal. The phenolsulfonphthalein excretion was 15 per cent in two hours; the serum albumin was 4.4, and the globulin, 1.5; the nonprotein nitrogen on admission was 43, and, terminally, 72; the carbon dioxide combining power terminally was 14.5. A roentgenogram revealed that the heart was enlarged in all diameters. The electrocardiogram revealed right axis deviation and incomplete auriculoventricular block; the latter was caused by digitalis.

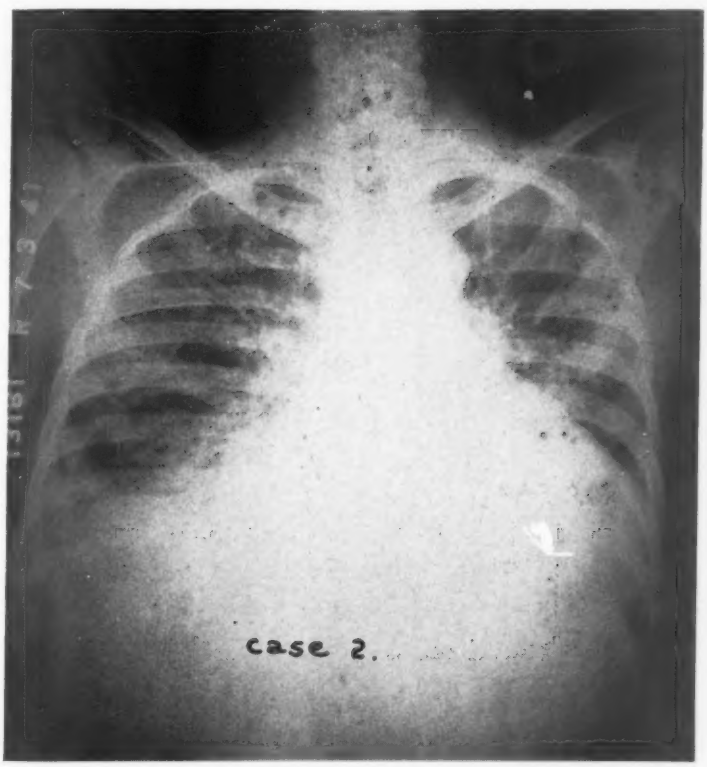

Fig. 4.—Case 2. Teleoroentgenogram, terminally.

At autopsy, clubbing of the fingers and toes and edema of the extremities were present. Examination of the brain revealed heterotopia of gray matter in the right centrum semiovale which was congenital. The lungs were congested, and, microscopically, terminal lobular pneumonia was found. The intestinal mucosa, spleen, and liver were congested. Microscopically, the liver showed the central fibrosis, atrophy, and congestion indicative of cardiac cirrhosis. The kidneys were small, with a finely granular surface and a narrowed cortex. The pelves were normal. Microscopically, the most significant change was marked arteriolar sclerosis, associated with a moderate increase in the fibrous stroma. Arteriolar thickening was noted also in the sections of liver, spleen, pancreas, duodenum, and adrenal gland.

The heart weighed 600 grams; it lay in the normal position. There were hypertrophy and dilatation of all four chambers. The pericardium was smooth and glistening. The myocardium of the left ventricle measured 20 mm. in thickness at the

base, 14 mm. midway to the apex, and 10 mm. at the apex. The myocardium of the right ventricle measured 16 mm. at the base, 14 mm. midway to the apex, and 10 mm. at the apex. On section of the myocardium, fibrous streaking was not visible grossly. The endocardial surfaces were, for the most part, smooth and glistening. An outpocketing of the interauricular septum, measuring about 2 cm., extended from the right atrium into the left. The edges of the outpocketing contained numerous small fenestrations, so that a communication between the atria existed. A valvular effect was obvious, by which these fenestrations were closed when the pressure in the left auricle exceeded that in the right. An interventricular septal defect, measuring 1.5 by 1.5 cm., was found at the most basal portion of the septum. The

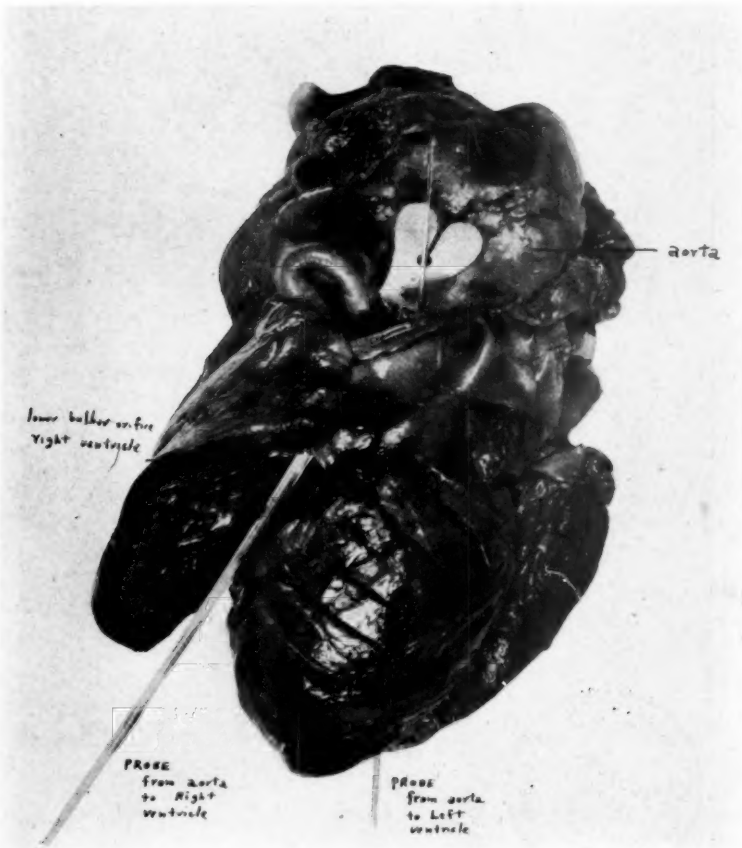

Fig. 5.—Case 2. Heart.

aorta overlay the septum, so that approximately two-thirds of its lumen was situated over the cavity of the right ventricle and one-third over the cavity of the left. The mitral, tricuspid, and aortic valves were entirely normal. The pulmonic valve was bicuspid. The valve leaflets were normal. The pulmonary artery measured 17 mm. in diameter at the valvular orifice. Beneath the pulmonic valve, the pulmonic conus was considerably thickened and fibrotic, and, at a point 15 mm. below the valve orifice, it narrowed down until it was approximately 6 by 10 mm. in diameter. The remnants of the ductus arteriosus were noted as a fibrous strand approximately 1 cm. long and 1 mm. wide, running between the aorta at a point 7 cm. above the valve orifice to the

pulmonic artery at a point 6.5 cm. above the valve orifice. No lumen could be distinguished grossly within this fibrous strand. At the site of its insertion into the aorta and pulmonary artery, small, shallow depressions were found. The coronary ostia were patent. The coronary arteries were of good caliber, and showed only slight atheromatous changes, with slight narrowing of the lumen in some areas. The aorta showed moderate atheromatous changes without ulceration or calcification. Microscopically, the ductus contained no definite lumen. The myocardium was moderately fibrotic.

COMMENT

The unusually long duration of life in the first case, 53 years, as well as the relative lack of cyanosis or decreased cardiac reserve until late in life, in spite of arduous physical labor, is, at first glance, rather difficult to understand. The heart itself provided a possible explanation for the patient's relatively good fortune. The pulmonic stenosis in this case was at the site of the valve itself. There was only slight narrowing of the lower bulbar orifice, which is the usual site for the pulmonic stenosis associated with the tetralogy. Abbott[2] stated that pulmonary valvular stenosis is, in these cases, "practically always inflammatory." Indeed, the appearance of the valve was characteristic of a chronic rheumatic process. We have further evidence of a rheumatic process in the pericarditis, the slight microscopic myocardial changes, the concomitant changes in the tricuspid valve, the microscopic fibrosis, and the vascularization and cellular infiltration of the valves and ventricular endocardium. Clinically, there was evidence of recurrent rheumatic infection. The conclusion seems justified that the pulmonic stenosis was, in this case, rheumatic in origin, and was probably acquired, judging from the history, some time after the age of 37 years.

Although the pulmonic stenosis was acquired, the other changes, specifically the interventricular septal defect and the dextroposition of the aorta, were manifestly congenital. This complex of congenital cardiac abnormalities, which differs from the tetralogy of Fallot fundamentally only in the absence of pulmonic stenosis, has been called the Eisenmenger complex,[4] and is considered by some as a variant of the tetralogy. It is much less common than the tetralogy, and, what is more important, the functional changes associated with it are of less serious prognostic significance. The difference in the cardiodynamics is as indicated in Figs. 6 and 7 (adapted from Abbott).

Fundamentally, the difference lies in the fact that, in the tetralogy, the pulmonic stenosis impedes the flow of venous blood into the pulmonary artery, forcing it, instead, to pass through the septal defect into the systematic circulation. This mechanism is lacking in the Eisenmenger complex. Much less venous blood passes into the aorta, directly or by way of the septal defect; a greater portion enters the relatively wide orifice of the pulmonary artery to be oxygenated in the lungs; less cyanosis is observed and, in general, the cardiodynamics more nearly approach the normal. The relatively large size of the pulmonary artery

in this case would further indicate that at some time a relatively large volume of blood had passed through it. If the pulmonic stenosis had been present since birth, the pulmonary artery would possibly have been small and hypoplastic, as it is in the typical tetralogy. Of course, other influences may well be related to the hypoplasia which occurs in such cases.

In retrospect, we believe that this man was born with what is commonly called the Eisenmenger complex. During the early portion of his life he suffered only the relatively minor cardiac embarrassment caused by this type of lesion. At a later date a rheumatic infection supervened, with resultant stenosis of the pulmonic valve. With the development of this pulmonary stenosis, all of the anatomic changes of the tetralogy of Fallot were established, and this was accompanied by a serious derangement in cardiodynamics. This contributed to his disability and death.

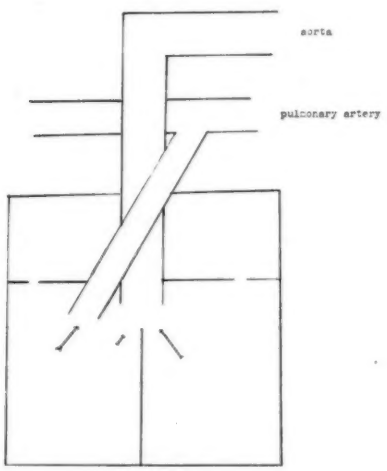

Fig. 6.

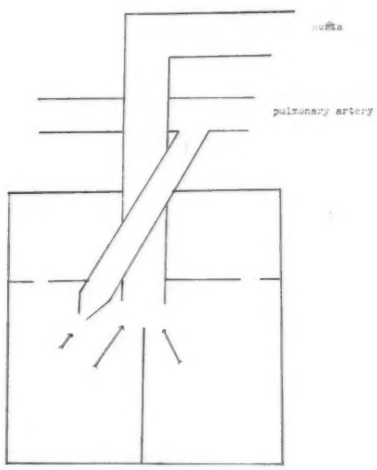

Fig. 7.

Fig. 6.—Case 1. Diagram. Circulation in Eisenmenger complex before rheumatic involvement.

Fig. 7.—Case 1. Diagram. Circulation in tetralogy of Fallot after rheumatic involvement.

Active pulmonary tuberculosis is not rare in such cases. Norris and Landis[5] reported that 160 of 440 patients with pulmonary stenosis, or 35 per cent, had active pulmonary tuberculosis at the time of death. In contradistinction, it is well known that patients with mitral stenosis have a comparatively low incidence of pulmonary tuberculosis.

The localization of the rheumatic infection in the right side of the heart in this case is of considerable interest. Its significance, however, is beyond the scope of this paper.

The second patient did not fare as well, either as to duration of life or symptoms. Nevertheless, there is no question that she was more fortunate than the average. One possible explanation for her relatively long life is suggested by the presence of the fibrosed remains of the

ductus arteriosus. Certainly, at the time of her death, and during the period when the ductus was fibrosed, it played no part in the altered dynamics. However, the persistence of the ductus to this age, even as a fibrous band, suggests the possibility that it might have remained patent after birth for a longer than normal period of time. While it was patent, and to the extent that it was patent, the ductus arteriosus served to alleviate the altered cardiodynamics by circumventing the stenotic pulmonary passage and permitting a greater volume of blood to enter the lungs. This is indicated in Fig. 8.

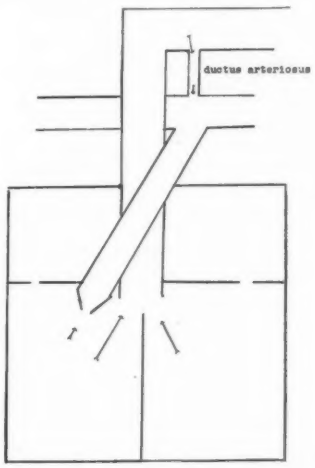

Fig. 8.—Case 2. Diagram. Effect of patency of ductus arteriosus on the circulation in the tetralogy of Fallot in early life (postulated).

Another factor which may have influenced the cardiodynamics is the systemic hypertension. This, in all probability, was the result of an unrelated acquired disease affecting the peripheral resistance, and bore no or little direct relation to central cardiac factors. The arteriolar lesions in the kidney were such as are ordinarily found in hypertension of vascular origin. In any case, the presence of increased pressure in the arteries and aorta would serve to increase the pressure within both the left and right ventricles (because of the marked dextroposition and the septal defect), at least during systole, and would thus increase the head of pressure at the narrowed pulmonic orifice. This would increase the flow of venous blood to the lungs. If the ductus arteriosus was patent, the passage of blood to the lungs would have been further facilitated. The presence and degree of systemic hypertension would tend to increase oxygenation of the blood and thus aid the patient.

The role of the patent foramen ovale is of questionable significance. The actual orifice was small, and the endocardial septa were so arranged as to possess a valvular action by which blood was permitted to pass only from right to left. In the normal heart, the pressure is somewhat greater in the left atrium than in the right. If this were true in this case, no

blood flow would occur. The decreased blood flow to the lungs, and therefore the decreased blood flow to the left auricle, may have resulted in a decrease or even a reversal in this pressure relationship. Congestive failure in this case would almost certainly have done so, and, therefore, we may assume that a small amount of blood did pass through the foramen ovale from the right to the left atrium, at least under some circumstances. This blood would then pass into the left ventricle rather than the right. The difference, however, is considered to be of only slight significance, inasmuch as the volume of blood under discussion is small, and the difference in the ultimate pathway of the blood from the two ventricles, conjoined as they were by a septal defect and a common (dextroposed) aorta, was also slight.

Roentgenologically, the tetralogy[6] is characterized by the small size of the hypoplastic conus, associated with narrowing of the lower bulbar orifice. The roentgenogram of the second patient (Fig. 4), although not characteristic, was of this general nature. It showed changes of the hypertensive type. The roentgenogram (Fig. 1) of the first patient showed the prominence of the pulmonic conus which is characteristic of the Eisenmenger complex.

SUMMARY

Two cases are presented, in which, at autopsy, there were changes in the heart which compose the tetralogy of Fallot, namely, right ventricular hypertrophy, pulmonic stenosis, interventricular septal defect, and dextroposition of the aorta. The patients were 53 and 43 years of age, respectively. The first, it is believed, orginally had an Eisenmenger variant, with no pulmonic stenosis. Rheumatic pulmonic valvulitis, acquired late in life, resulted in pulmonic stenosis, completing the tetralogy and contributing greatly to his disability and death. The second patient had the true tetralogy from birth. The presence of patency of the ductus arteriosus, and, later, of systemic hypertension, may have helped alleviate the cardiodynamic derangement and contributed to her longevity.

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MYOCARDIAL INFARCTION INDICATED BY AN ELECTROCARDIOGRAPHIC PATTERN IN WHICH T_1 IS LOWER THAN T_3

Report of 45 Cases

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MYOCARDIAL infarction is signified in the electrocardiogram by a high take-off of the S-T segment and later by inversion of the T wave. These signs may be accompanied by changes in the size and shape of the QRS complex. In the presence of anterior wall infarction, the significant changes appear in Lead I. They are often associated with reciprocal changes in Lead III; that is, elevation of the S-T segment and inversion of the T wave in Lead I may be accompanied by depression of the S-T segment and by an upright T, which is sometimes of unusual height, in Lead III. The reciprocal changes do not always parallel the significant changes; they are often less pronounced or may be absent. Even then, high take-off of the S-T segment and inversion of T in Lead I are sufficient evidence of anterior wall infarction.

The interest of clinicians has been focused mainly upon the significant changes. In some instances of anterior wall infarction, however, the signs in Lead I are poorly developed or occur rather late. The elevation of the S-T segment may be inconspicuous or absent; and, instead of sharp inversion, there is sometimes but slight flattening of the T wave, which remains upright or becomes isoelectric. The flat, upright T_1 may display a slight central dip, so that an M-shaped T wave results,[1] or the dip may appear at the end of the positive T wave. When the significant changes are poorly developed, the reciprocal alterations in Lead III are often marked and predominant. A distinct depression of the S-T segment is sometimes noted in Leads II and III in the absence of elevation of S-T in Lead I. More often, the prominent change is an increase in the voltage of T_2 and T_3.

The diagnostic significance of the reciprocal changes has received but scant attention. Zwillinger[2] has expressed the opinion that an isoelectric T_1, associated with a positive T_2 and T_3, may signify anterior wall infarction. Ashman and Hull[3] have pointed out that sharp reduction in the height of T_1 and elevation of T_3, together with a marked decrease in the amplitude of QRS in the standard leads, occasionally represent the only signs of anterior wall infarction. Bohning and Katz[4] have stressed the diagnostic significance of "upright coronary T waves" in Leads II and III in the presence of anterior wall

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infarction. These T waves are mirror images of inverted coronary T waves. We, too, have occasionally found this sign useful in the diagnosis of anterior wall infarction. More numerous are the cases in which myocardial infarction is indicated merely by a reversal of the ratio of voltage of T_1 and T_3, in the absence of inversion or marked enlargement of the T waves. Under normal conditions, except when the heart is perpendicular, T_1 is of greater amplitude than T_3. Reversal of this ratio has, in our experience, proved to be a valuable sign of myocardial infarction.

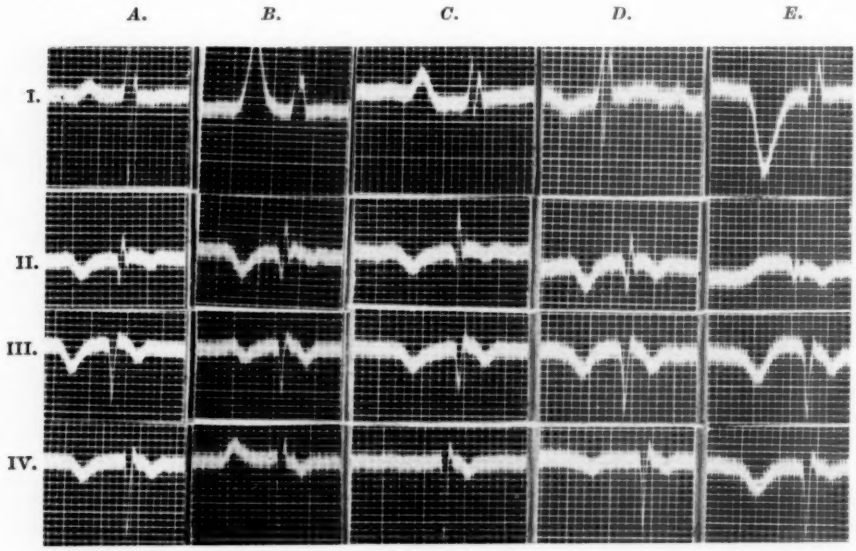

Fig. 1.—Case 1. *A*, Three hours after a severe anginal attack. The S-T segment is depressed in Leads II and III, and there is no corresponding elevation in Lead I. T_3 is nearly isoelectric. There is a deep Q wave and a high T wave in Lead IV.

B, Thirteen hours after the attack. The depression of the S-T segment in Leads II and III has subsided. T_1 has become flatter, and T_3 upright, resulting in the pattern $T_1<T_3$. A W-shaped QRS complex is visible in Lead IV and T_4 is of low voltage.

C, Five days after the attack. The S-T segment in Lead I is slightly convex, and a dip has appeared at the end of T_1. There is sharp inversion of T_4.

D, Five weeks after the attack. T_1 is inverted and there is a marked increase in the voltage of the negative T_1.

E, Four and a half months after the attack. T_1 has become positive again. The inverted T_1 has decreased in voltage.

CASE REPORTS

CASE 1.—H. L., a white man, aged 50 years, had suffered from hypertension for many years. On Sept. 22, 1939, while playing cards, he was seized by severe precordial pain which radiated to the left shoulder and arm, and burst into a cold sweat. The next day he had a leucocytosis of 13,850, and his blood pressure had fallen to 90/70.

The first electrocardiogram (Fig. 1*A*) was taken three hours after the onset of the attack. It showed distinct depression of the S-T segment in Leads II and III, but no conspicuous elevation of S-T in Lead I. The precordial lead showed a deep Q wave and an upright T of marked amplitude. Thirteen hours after the attack (Fig. 1*B*), the depression of S-T in Leads II and III had disappeared; T_1 was now distinctly flattened, whereas T_3 had grown high so that reversal of the ratio of amplitude of T_1 and T_3 resulted. A W-shaped QRS complex had developed in the precordial lead, and T_4 was markedly reduced in voltage.

Five days after the attack (Fig. 1*C*), a slight convexity of the S-T segment and a shallow dip at the end of the T wave were noted in Lead I. The T waves in Leads II and III were upright, but not of unusual voltage. In the precordial lead sharp inversion of the T wave had developed. An electrocardiogram taken five weeks after the attack (Fig. 1*D*) showed distinct inversion of T_1 and a marked increase in the voltage of the inverted T wave in Lead IV. Four and a half months after the attack (Fig. 1*E*), the T wave in Lead I had turned positive and was equal in voltage to T_3. A shallow, inverted T wave was visible in Lead IV.

Comment.—Myocardial infarction was indicated thirteen hours after the onset of the anginal attack by reversal of the ratio of voltage of T_1 and T_3; there were also significant changes in Lead IV. A remarkable feature was the initial depression of the S-T segment in Leads II and III, in the absence of a corresponding high take-off in Lead I.

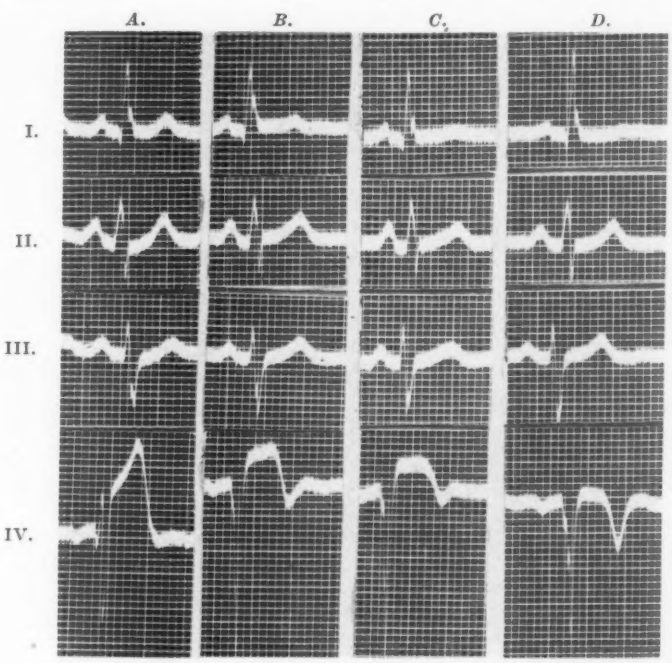

Fig. 2.—Case 2. *A*, On the day when the patient had suffered two severe anginal attacks. Besides left axis deviation and slurring of QRS in the standard leads, there are a high take-off of the S-T segment and marked increase in the voltage of T in Lead IV.

B, One day after the attacks. T_1 has decreased in voltage and T_3 is slightly higher, resulting in the pattern $T_1<T_3$. The R wave has disappeared and the T wave has become inverted in Lead IV.

C, Four days after the attacks. T_1 is even more flattened.

D, Four and one-half months after the attacks. T_1 is almost isoelectric and T_3 is positive. There is sharp inversion of T_4.

Case 2.—C. W., a white man, aged 51 years, on Jan. 8, 1939, felt a sharp pain in the left scapular region while pulling a drunkard out of his car. On the following day a few short attacks of pain occurred. On January 10, the patient was seized by an anginal attack of greater severity; he became cyanotic and perspired profusely. On January 12, he had two more attacks of violent pain which required the administration of morphine.

The first electrocardiogram was taken January 12 (Fig. 2*A*). It showed, in addition to left axis deviation, slurring of QRS in the standard leads, and elevation of the S-T segment in the precordial lead. On the following day, January 13 (Fig. 2*B*), the T wave in Lead I had become flat, and its amplitude was less than that of T_3. Simultaneously, the R wave in the precordial lead disappeared, and inversion of T_4 developed. In the next tracing, taken January 16 (Fig. 2*C*), T_1 was more flattened. Reversal of the ratio of amplitude of T_1 and T_3 was still visible in a tracing taken after four and a half months (Fig. 2*D*).

Comment.—Myocardial infarction was indicated twenty-four hours after the anginal attack by the electrocardiographic pattern $T_1 < T_3$, and also by significant changes in Lead IV. These signs were still present four and a half months after the attack.

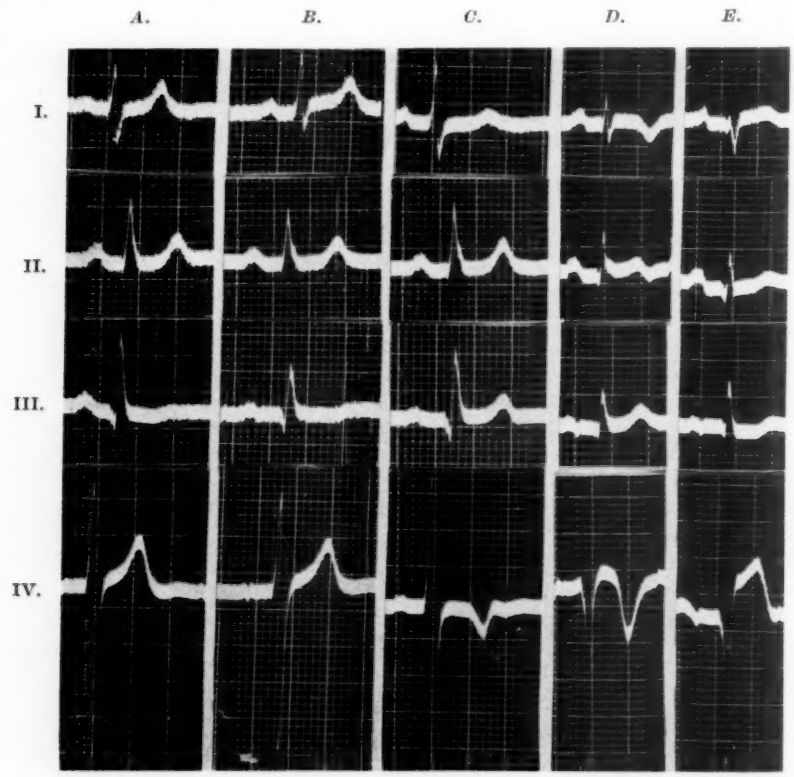

Fig. 3.—Case 3. *A* and *B* were taken at the time when the patient suffered from severe angina pectoris of effort, not of rest. There were no significant changes in the electrocardiogram.

C, Five weeks later, when the patient suffered numerous brief anginal attacks during rest, relieved by nitroglycerin. T_1 has become flattened and T_3 upright, resulting in the pattern $T_1 < T_3$; also, inversion of T_4 has developed.

D, One day after a severe, long anginal attack, followed by a pericardial friction rub. There are low voltage of QRS and slight elevation of S-T in the standard leads. T_1 is inverted. In the precordial lead, the R wave has disappeared and T_4 has become sharply inverted.

E, Two days following a fresh severe anginal attack. A large Q wave has appeared in Lead I. The S-T segment is slightly elevated in Lead I and depressed in Lead III. In Lead IV, marked elevation of S-T has developed and T_4 has become upright.

CASE 3.—B. J., a white man, aged 64 years, in February, 1932, after pushing his car, suffered an attack of severe precordial pain which lasted several hours. Myocardial infarction was diagnosed. After this attack recovery was complete, and the patient was able to walk as many as fifty blocks without experiencing discomfort.

In March, 1941, pain in the precordial region occurred again during walking; the patient was not able to walk more than two or three blocks without experiencing anginal pain. Two electrocardiograms, taken March 11 and 18, 1941 (Fig. 3*A* and *B*), failed to reveal significant abnormalities. A diagnosis of impending infarction was made. The sedimentation rate (Westergren) was 68 mm. on March 12.

Early in April, 1941, the attacks of pain grew more severe; they came on even during rest, frequently at night, and lasted from ten to twenty minutes. They were promptly relieved by nitroglycerin. The patient was advised to stay at home, but, even then, he suffered ten to twelve attacks every day. An electrocardiogram taken April 24, 1941 (Fig. 3*C*), showed distinct flattening of T_1, together with an increase in the voltage of T_3. Also, inversion of the T wave had developed in the precordial lead. In spite of complete rest in bed, protracted attacks of severe precordial pain occurred April 30, and the administration of morphine was required. A pericardial friction rub was heard on the following day. An electrocardiogram taken May 1 (Fig. 3*D*) showed inversion of T_1 and low voltage of QRS in the standard leads; R_1 had disappeared and inversion of T_4 was more pronounced. Another violent attack occurred May 10, and was followed by pulmonary edema. An electrocardiogram taken May 12 (Fig. 3 *E*) displayed a large Q wave and slight elevation of S-T in Lead I; a high take-off of the S-T segment, with an upright T, was present in Lead IV. The patient died on May 22, 1941.

Post-mortem examination revealed marked arteriosclerosis of the coronary arteries. The ramus descendens anterior of the left coronary artery was occluded by an old thrombus. The right coronary artery was almost completely obstructed by calcified deposits. The apical region of the left ventricle was thinned; its muscle was replaced by whitish fibrous tissue. There were also large areas of yellowish discoloration, with hemorrhages, indicating recent infarction, in the lateral wall of the left ventricle and in the interventricular septum. Whitish streaks of fibrosis were also visible in the posterior wall of the left ventricle.

Comment.—Progressive coronary insufficiency during the last two months of life caused repeated myocardial infarctions, as shown by necropsy. The second phase of the disease, initiated by brief anginal attacks during rest, was characterized in the electrocardiogram by reversal of the ratio of amplitude of T_1 and T_3 (Fig. 3*C*).

CASE 4.—S. M., a white woman, aged 60 years, was admitted to the hospital September 26, 1941, after she had suffered brief attacks of precordial pain during rest, for six weeks. Examination revealed marked hypertrophy of the left ventricle, as indicated by a broad, heaving apex beat. The heart sounds were fair, and no bruits were audible. During the first few days after admission the temperature rose to 100.2° F. The blood pressure, which had previously been high, according to the history, measured 136/74 on admission. The leucocyte count was 10,600 on September 27. The sedimentation rate (Westergren) was 23 mm.

An electrocardiogram on September 29 (Fig. 4*A*) showed, besides left axis deviation, an almost isoelectric T in Lead I; an upright T wave of high voltage, exhibiting the features of the "upright coronary T waves," was present in Leads II and III. T_4 was inverted. During the following three weeks three electro-

cardiograms were taken (Fig. 4*B*, *C*, and *D*); they showed only slight variations. T_1 became temporarily negative (Fig. 4*C*). Reversal of the ratio of voltage of T_1 and T_3 remained the predominant feature of the electrocardiogram.

Comment.—The history of repeated anginal attacks during rest, and the rise in temperature, leucocytosis, and increased sedimentation rate indicated myocardial infarction. In the electrocardiogram this diagnosis was supported by the pattern $T_1 < T_3$, and by inversion of T_4.

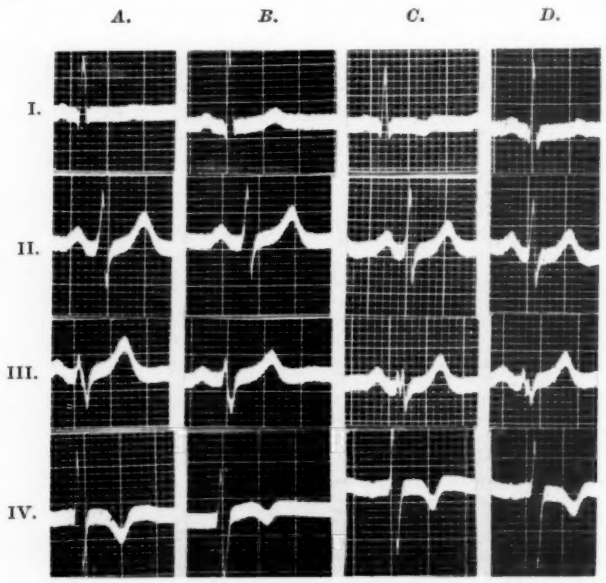

Fig. 4.—Case 4. *A*, For six weeks prior to the examination there were numerous brief anginal attacks during rest. T_1 is almost isoelectric, whereas T_2 and T_3 are upright and high ("upright coronary T waves"), resulting in the pattern $T_1<T_3$. T_4 is inverted.

B, after seven days, T_1 is upright and still smaller than T_3.

C, after nineteen days, T_1 has become inverted.

D, after twenty-one days, T_1 is upright again; the pattern $T_1<T_3$ is still present.

Case 5.—H. R., a white man, aged 60 years, had suffered from substernal pain since the middle of 1941. The attacks came on while he was walking, and subsided after a few minutes of rest. In August, 1941, the patient was seized by severe precordial pain which lasted for a few days. He was hospitalized, and myocardial infarction was diagnosed. In December, 1941, the patient again suffered several anginal attacks at night, each lasting about ten minutes. The sedimentation rate was 50 mm. (Westergren) on December 13. An electrocardiogram (Fig. 5*A*), on December 12, showed low voltage of QRS in the standard leads; T_1 was nearly isoelectric, and T_2 and T_3 were positive and high. The T wave in the precordial lead was sharply inverted.

Comment.—The history of repeated attacks of severe anginal pain during rest suggested past and recent myocardial infarction. The electrocardiographic pattern $T_1 < T_3$, associated with low voltage of QRS and inversion of T_4, supported this diagnosis.

CASE 6.—A. S., a white man, aged 52 years, in 1934 had had an attack of severe precordial pain during rest, associated with a fainting feeling, cold sweat, and vomiting. Two injections of morphine were required, and the patient was hospitalized. Thereafter, anginal pain was often felt on exertion and occasionally during rest. When the patient was first examined by us on Nov. 7, 1939, his electrocardiogram (Fig. 5*C*) showed upright T waves in the standard leads; T_1 was lower than T_3. In the precordial lead a W-shaped QRS complex was noted, and the T wave was diphasic. Two other tracings, taken May 17, 1940 (Fig. 5*D*), and Dec. 2, 1940 (Fig. 5*E*), showed the same reversed ratio in the voltage of the T waves in Leads I and III. T_4 in the last tracing was sharply inverted.

Comment.—Myocardial infarction which, according to the history, had been sustained six years earlier, was indicated in the electrocardiogram by the pattern $T_1 < T_3$, and by significant changes in the precordial lead.

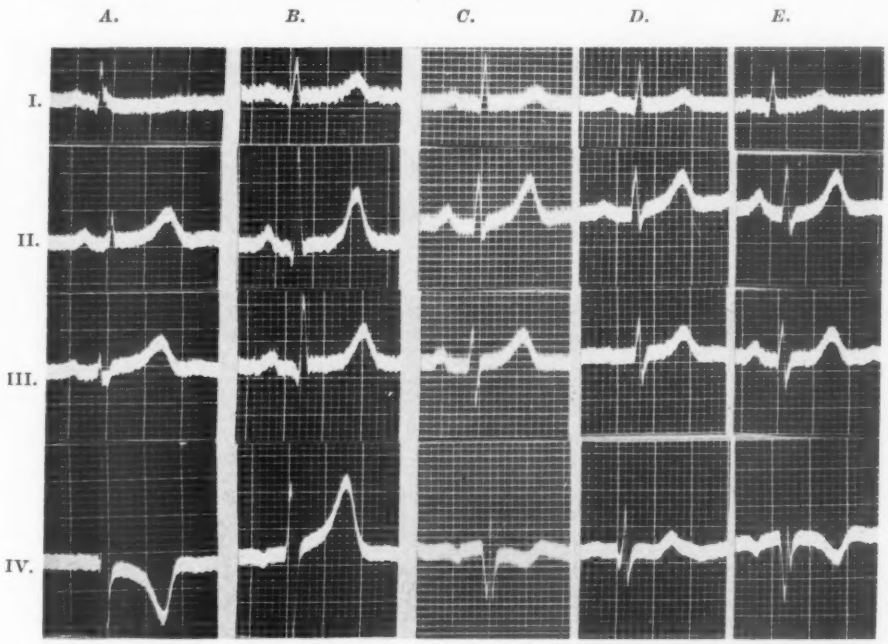

Fig. 5*A*.—Case 5. After repeated severe anginal attacks. T_1 is almost isoelectric. T_2 and T_3 are upright and rather high, resulting in the pattern $T_1<T_3$. T_4 is sharply inverted. There is low voltage of QRS in the standard leads.

Fig. 5*B*.—Case 7. Sixteen years previous to the examination the patient had suffered a severe anginal attack, with collapse. All T waves are upright. T_1 is of normal voltage, but T_2 and T_3 are abnormally high ("upright coronary T waves"), resulting in the pattern $T_1<T_3$. The precordial lead is normal.

Fig. 5*C*, *D*, and *E*.—Case 6. Six years prior to examination there was an attack of severe precordial pain, with faintness and collapse. All three tracings (*C*, *D*, and *E*), taken at intervals of about six months, show the pattern $T_1<T_3$. In the precordial lead there are significant changes; QRS is W-shaped and the T wave diphasic or inverted (in *E*).

CASE 7.—D. R. was a white man, 70 years of age. Sixteen years earlier, while walking in the street, he suddenly felt a severe pain substernally and collapsed. Thereafter, he was confined to bed for six weeks. The patient had to give up his work because he frequently suffered anginal pain on exertion and occasionally even during rest. The pain was promptly relieved by nitroglycerin.

TABLE I

ANALYSIS OF 45 CASES IN WHICH THERE WAS THE ELECTROCARDIOGRAPHIC PATTERN $T_1 < T_3$, WITH SYMPTOMS AND SIGNS SUGGESTIVE OF MYOCARDIAL INFARCTION

CASE 1. H. L.	AGE	SEX	ANGINA PECTORIS OF EFFORT	SYMPTOMS AND SIGNS SUGGESTING MYOCARDIAL INFARCTION	ELECTROCARDIOGRAM		COMPLICATING CONDITIONS	NECROPSY OBSERVATIONS
					T_1/T_3 VOLTAGE IN MM.	OTHER CHANGES		
	50	♂		Attack of severe precordial pain with cold sweat, followed by leucocytosis and fall in blood pressure	1.1/3.0	Progressive changes. Temporary inversion of T_1. W-shaped QRS and inversion of T in Lead IV	Hypertension	
2. C. W.	51	♂		Several severe attacks of anginal pain requiring morphine	0.8/2.0	Progressive changes. Elevation of S-T, absence of R and inversion of T in Lead IV		
3. B. J.	64	♂	6 weeks	Repeated attacks of severe and protracted anginal pain, followed by rise in temperature and increased sedimentation rate	1.4/2.0	Progressive changes significant of anterior wall infarction		Fibrosis and thinning of the apical region of the left ventricle. Recent infarction in the interventricular septum and lateral wall of the left ventricle. Areas of fibrosis in the basal portion of the posterior wall of the left ventricle
4. S. M.	60	♀		Repeated brief attacks of precordial pain occurring at rest, followed by precordial tenderness, rise in temperature, leucocytosis, and increased sedimentation rate	0.3/4.0	Transient inversion of T_1. Inversion of T_4. "Upright coronary T waves"		

5. H. R.	60	♂	6 months	Severe attack of precordial pain, followed by increased sedimentation rate. Patient was admitted to a hospital where anterior wall infarction was diagnosed	0.5/3.4	Sharply inverted T_4		
6. A. S.	52	♂	6 years	Attack of severe precordial pain, with collapse, cold sweat, and vomiting	1.2/3.8	W-shaped QRS and inversion of T in Lead IV		
7. D. R.	70	♂	16 years	Attack of severe precordial pain, with collapse. Patient was then confined to bed for 6 weeks	2.0/4.0	"Upright coronary T waves" in Leads II and III	Intermittent claudication	
8. M. L.	73	♂		Within 20 months four attacks of precordial pain, lasting up to 20 hours, and followed by rise in temperature and increased sedimentation rate	2.0/2.8	Diphasic (minus-plus) T wave of low voltage in Lead IV		
9. S. S.	59	♂	6 years	Long attack of severe precordial pain with cold sweat	0/1.5	Progressive changes. Temporary inversion of T_1 and sharp inversion of T_4	Diabetes, hypertension, intermittent claudication	
10. S. G.	47	♂	1½ years	Attack of sharp precordial pain, with subsequent, lasting fall in blood pressure	1.0/2.0	Progressive changes. Elevation of S-T and sharp inversion of T in Lead IV		
11. S. K.	62	♂		Attack of severe precordial pain, not relieved by morphine, and lasting for 2½ days	2.0/2.8			
12. A. K.	55	♂	13 months	Attack of severe precordial pain, followed by confinement to bed for 12 weeks	0.7/1.3	Progressive changes. Temporary inversion of T_1. W-shaped QRS and inversion of T in Lead IV		
13. D. B.	54	♂		Repeated attacks of pain in the epigastrium and beneath the sternum, the last attack followed by rise in temperature and drop of blood pressure	0/2.0			

TABLE I—CONT'D

CASE	AGE	SEX	ANGINA PECTORIS OF EFFORT	SYMPTOMS AND SIGNS SUGGESTING MYOCARDIAL INFARCTION	ELECTROCARDIOGRAM		COMPLICATING CONDITIONS	NECROPSY OBSERVATIONS
					T_1/T_3 VOLTAGE IN MM.	OTHER CHANGES		
14. S. R.	56	♂	6 years	Severe attack of precordial pain, with profuse perspiration, lasting for one hour. Morphine was given and patient was confined to bed for 6 weeks	0.8/2.0	Diphasic (minus-plus) T wave of low voltage in Lead IV		
15. F. L.	60	♀	8 weeks	Nocturnal attacks of violent precordial pain, followed by increase in sedimentation rate	1.4/2.2	S-T depressed and upright T of low voltage in Lead IV		
16. M. S.	65	♀	2 years	Attack of violent precordial pain lasting for 2 hours, followed by increased sedimentation rate	1.0/1.5	Diphasic (minus-plus) T wave of low voltage in Lead IV	Hypertension	
17. J. B.	70	♂		Attack of severe pain in the precordium and epigastrium, followed by repeated attacks of burning pain which were relieved by belching. Increase in sedimentation rate	0.7/1.2		Hypertension	
18. W. L.	50	♂		Severe substernal and epigastric pain, with cold sweat following an automobile accident	0/2.0	Low voltage of QRS in Lead I. Conspicuous Q_2 and Q_3		Coronary arteriosclerosis. Old healed infarction in the apical area and anterior wall of the left ventricle. Scattered areas of fibrosis throughout the myocardium
19. M. F.	53	♂		Several attacks of precordial pain, each lasting for a few hours, within the preceding 2 years	0.8/2.0			

20. E. C.	65	♂		For the preceding 2 months, slight effort caused marked shortness of breath. The patient had always been well previously, and was accustomed to hard work	0/1.2	Low voltage of QRS in the three standard leads. Absence of R and inversion of T in Lead IV		
21. H. G.	63	♂		Two weeks after an abdominal operation, repeated attacks of severe precordial pain occurred during rest, followed by rise in temperature and increased sedimentation rate	1.5/2.0	Progressive changes. Flattening of T_4 which finally turned diphasic		
22. N. W.	47	♂	1 year	Attack of precordial pain, with collapse; pain lasted for 24 hours	0.8/2.0			
23. H. P.	60	♀	2 years	Attack of violent precordial pain lasting a whole night	0.8/2.0	Low voltage of QRS in Lead I. Sharp inversion of T_4	Hypertension	
24. J. G.	43	♂	2 years	Following a cold, sharp precordial pain developed, lasting for 2 hours, followed by rise in temperature	0.7/1.3	Significant Q_1; W-shaped QRS and inversion of T in Lead IV		
25. H. J.	51	♂		Attack of severe pressure in the precordium, with collapse and cold sweat, followed by increased sedimentation rate	0.5/4.0	Sharp inversion of T_4		
26. B. S.	59	♂	1 year	Attack of excruciating precordial pain, requiring morphine, followed by rise in temperature	0.8/3.0	Progressive changes. Temporary inversion of T_1. Absence of R and inversion of T in Lead IV	Intermittent claudication	
27. M. D.	52	♂		Repeated attacks of sharp precordial pain of 15 minutes' duration for 2 weeks	0.5/3.0	Sharp inversion of T_4		
28. J. Z.	55	♂	1 year	Attack of violent, constricting chest pain lasting several hours, with vomiting	0.8/2.5	W-shaped QRS and inversion of T in Lead IV		
29. J. K.	51	♂	2 years	Attack of severe precordial pain lasting several hours, followed by rise in temperature	0/1.8	Absence of R, elevation of S-T, and beginning inversion of T in Lead IV		

TABLE I—CONT'D

CASE	AGE	SEX	ANGINA PECTORIS OF EFFORT	SYMPTOMS AND SIGNS SUGGESTING MYOCARDIAL INFARCTION	ELECTROCARDIOGRAM		COMPLICATING CONDITIONS	NECROPSY OBSERVATIONS
					T_1/T_3 VOLTAGE IN MM.	OTHER CHANGES		
30. E. P.	49	♂	4 years	Attack of severe precordial pain of 4 hours' duration, with profuse perspiration	0.5/3.5			
31. J. K.	57	♀	3 weeks	Sudden onset of severe angina pectoris of effort, 3 weeks prior to examination. The patient was not able to walk more than one block. Increase in sedimentation rate	0/3.0	Progressive changes. Sharp inversion of T_4	Hypertension	
32. P. S.	52	♂	2 months	Attack of violent precordial pain, with cold sweat lasting ½ hour, followed by increase in sedimentation rate	0/1.3	Progressive changes. Sharply inverted T_4		
33. B. B.	47	♂		Attack of severe precordial pain, with collapse	0.8/2.5	Progressive changes. Inversion of T_4		
34. W. L.	48	♂	4½ months	Attack of severe precordial pain lasting 15 minutes, in two successive nights	0.7/1.3	Inversion of T_4		
35. J. S.	52	♀	4 months	Severe effort angina, with sharp onset on a certain day. The patient was unable to walk more than ½ block. Rapid sedimentation rate	0/3.0	Progressive changes. Temporary inversion of T_1. Sharp inversion of T_4		
36. J. F.	68	♂	5 months	Repeated attacks of precordial pain during rest, lasting about 15 minutes. Leucocytosis	0/1.0	W-shaped QRS and inversion of T in Lead IV		
37. S. S.	65	♂	7 years	Severe attack of precordial pain requiring morphine, followed by frequent anginal attacks. The patient was repeatedly hospitalized because of such attacks	0.3/1.5	Significant Q_1; very small R_4	Hypertension	
38. L. L.	61	♀	2 years	Prolonged attack of violent precordial pain, followed by increased sedimentation rate	0.3/1.1	Diphasic (plus-minus) T_4	Diabetes	

39. J. A.	63	♂		Attack of severe precordial pain during rest, lasting about 15 minutes, and anginal attacks during subsequent nights, followed by leucocytosis	1.0/2.0			
40. J. H.	45	♂		Attack of precordial pain radiating to the left arm, of several hours' duration	1.0/1.3	Absence of R and sharp inversion of T in Lead IV		
41. W. H.	25	♂		Attack of severe precordial pain, radiating to the left arm, lasting 24 hours	0.6/1.3	Progressive changes. Elevation of S-T and sharp inversion of T in Lead IV	Rheumatic heart disease. Subacute bacterial endocarditis	
42. H. F.	49	♂		Severe pain in the precordial region and left arm, lasting 2 hours, followed by leucocytosis, rise in temperature, and increased sedimentation rate	0.4/1.2	Progressive changes. Low voltage of QRS in the standard leads. Inversion of T_4		
43. H. J.	52	♂	1 year	Following an abdominal operation, repeated attacks of substernal pressure and numbness in both arms, with profuse perspiration. The attacks lasted about 10 minutes. Subsequently, there was rise in temperature and increased sedimentation rate	0/3.3	Progressive changes. Inversion of T_4	Hypertension	
44. B. F.	60	♀	2 years	Attack of violent precordial pain during night followed by rise in temperature, fall in blood pressure, and increased sedimentation rate	0.8/1.3	Progressive changes	Hypertension	
45. D. D.	71	♂	2 years	Attack of severe pain in left arm and precordium lasting several hours. Subsequently, rise in temperature, leucocytosis, and increased sedimentation rate	0.3/2.0	Progressive changes. Lowering and part inversion of T_4		

The patient was admitted to the hospital in July, 1942, because of arteriosclerotic ulcerations of his toes. He did not complain of anginal pains at that time. Routine electrocardiographic examination (Fig. 5*B*) revealed the pattern $T_1 < T_3$ and "upright coronary T waves" in Leads II and III. This aroused a suspicion of myocardial infarction which was borne out by the history.

Comment.—Myocardial infarction sixteen years prior to examination was indicated in the electrocardiogram by the pattern $T_1 < T_3$.

Table I presents the clinical and laboratory data on forty-five patients who showed the electrocardiographic pattern $T_1 < T_3$ together with other evidence suggestive of myocardial infarction. Only tracings without inversion of the T waves were considered as fitting into the pattern $T_1 < T_3$. In all cases except one, a clinical diagnosis of coronary arteriosclerosis and ischemic myocardial necrosis was made. One patient (Case 41) had rheumatic heart disease and subacute infectious endocarditis. He had an attack of severe pain in the chest, followed by significant electrocardiographic changes; the attack was interpreted as due to coronary embolism. This patient was 25 years old, the youngest in our series. In the arteriosclerotic group, the ages ranged from 45 to 73 years. Thirty-seven of our patients were men, and eight were women.

All but one of the patients had a history of angina pectoris. Forty-two patients had had one or more attacks of severe precordial pain during rest; in nineteen cases, the attacks were protracted, lasting from a half-hour to a few days. Angina pectoris of the effort type was present in twenty-seven cases. In twenty-three cases, the anginal attacks were followed by a rise in temperature, leucocytosis, rapid sedimentation rate, or a fall in blood pressure, or by a combination of these signs. An increased rate of sedimentation was most frequently observed. Two patients (Cases 31 and 35) gave a history of angina pectoris of effort, but not at rest. They remembered accurately the date of onset of their pains, which were of marked intensity and occurred after walking only one block or less. According to our experience, these signs usually point to ischemic myocardial necrosis. One patient (Case 20) gave no history of angina pectoris. He complained only of marked shortness of breath that had developed suddenly two months before. Electrocardiographic examination showed the pattern $T_1 < T_3$ and absence of R_4 and inversion of T_4.

As has been mentioned, the electrocardiographic pattern $T_1 < T_3$ was present in all cases, either during the acute phase, after severe anginal pain, or as a persistent sign of chronic, irreversible myocardial changes. T_1 was upright in thirty-two cases and isoelectric in thirteen. In two instances the upright T_1 was M-shaped, and four times its positive portion was followed by a shallow negative phase. The upright T_1 was usually of low amplitude; only in two cases was its amplitude 2 mm.; in twenty-seven cases it was less than 1 mm.; and in sixteen cases

it ranged from 1 to 2 mm. Serial electrocardiographic examination showed a negative T wave in Lead I in nine cases.

Significant changes in the QRS complex were infrequent. A Q wave of significant size was observed twice in Lead I and once in Leads II and III. Low voltage of QRS in Lead I was present in five cases; low voltage in all standard leads was noted in nine instances. None of our patients had marked intraventricular block. Slight elevation of the S-T segment in Lead I was observed in one case only. Slight depression of the S-T segment in Lead I was present in five cases; marked depression of S-T in Leads II and III was observed in four instances.

The amplitude of the positive T wave in Lead III was almost invariably above the average, which, according to various authors,[3, 5-7] has been estimated as from minus .74 to plus 1.22 mm. In eight of our cases the amplitude of T_3 was more than 3 mm. The maximum amplitude was 4 mm. (three instances). Two patients had "upright coronary T waves" in Leads II and III.

The precordial lead was normal in nine cases. The majority of our patients showed changes in the QRS complex or T wave or both, such as usually accompany anterior wall infarction. The R wave in Lead IV was absent or of abnormally low voltage in twelve cases; in eight of these there was a W-shaped QRS complex. Abnormal elevation of the S-T segment was noted in two instances; slight depression of S-T was present in one case. The most frequently anomaly in Lead IV was inversion of the T wave (twenty-four cases); in fifteen cases, this was the only change in Lead IV. In two instances, T_4 was upright but of abnormally low voltage; in five cases, it was of low amplitude and diphasic (minus-plus).

DISCUSSION

Edeiken and Wolferth,[8] who studied the significance of low voltage T waves in Lead I (less than 2 mm. high), have stated that the voltage of T_1 is influenced by the position of the heart and diaphragm. When the heart is vertically placed, T_1 is sometimes low in the absence of heart disease, and is then usually associated with a low R_1. Roentgenologic study of the chest is therefore considered essential for the diagnostic evaluation of a low T_1. When, however, a low T_1 is associated with a normal or high R wave in Lead I, this is, according to Edeiken and Wolferth, strong indication of cardiac abnormality, especially of hypertensive heart disease.

Ashman and Hidden[9] have pointed out that the ratio of voltage of T_1 and T_3, rather than absolute measurement, is diagnostically important. The electrical axis of QRS must be considered in the diagnostic evaluation of the ratio of voltage of T_1 and T_3. Right axis deviation of QRS tends to be associated with right axis deviation of T ($T_1 < T_3$). This happens even in the absence of heart disease when the electrical axis of QRS forms an angle greater than plus 30°; when the angle is

less than plus 30° the pattern $T_1 < T_3$ indicates cardiovascular disease. In 80 per cent of such cases, as observed by Ashman and Hidden, right axis deviation of T was associated with hypertensive arteriosclerotic heart disease, and, in 10 per cent, with cardiovascular syphilis. It was rarely noted with other conditions, such as thyrotoxic heart disease (2.5 per cent), rheumatic heart disease (2 per cent), congenital heart disease (0.4 per cent), nephritis (0.8 per cent), and anemia (0.4 per cent).

Of our group of cases the pattern $T_1 < T_3$ was associated with dependable evidence of myocardial infarction in 75 per cent (thirty-four cases). As dependable evidence we have considered (1) protracted attacks of anginal pain, followed by a rise in temperature, leucocytosis, increased sedimentation rate, or a fall in blood pressure; (2) progressive electrocardiographic changes after attacks of anginal pain; and (3) absence or abnormally low voltage of R_4, associated with inversion of T_4. In two of our cases in which necropsy was obtained, there was evidence of old and recent infarction of the left ventricle, involving mainly the anterolateral wall and the interventricular septum. Necropsy observations, however, did not yield conclusive evidence as to the diagnostic significance of the electrocardiographic pattern $T_1 < T_3$, for the pathologic process underlying that pattern did not usually lead by itself to a fatal outcome. Death was the result of new, superimposed pathologic events which caused additional changes in the electrocardiogram, such as a deep Q wave, or high take-off of the S-T segment and inversion of T. In one case, reported by Zwillinger,[2] post-mortem examination revealed anterior wall infarction; the only electrocardiographic anomaly was an isoelectric T_1, accompanied by a positive T_3.

In eleven cases (25 per cent) of our series there was no dependable evidence of myocardial infarction; this possibility, however, was suggested by a history of severe angina pectoris of effort and at rest, and often by the presence of an inverted T wave in the precordial lead. Thus, the evidence seems to indicate that in the majority, if not in all, of our cases, recent or past myocardial infarction was the cause of the electrocardiographic pattern $T_1 < T_3$. The frequent coincidence of this pattern with electrocardiographic changes in the precordial lead indicative of anterior wall infarction suggests that the pattern $T_1 < T_3$ is probably equivalent to the T_1 type of myocardial infarction.

Reversal of the ratio of voltage of T_1 and T_2 is probably not caused by extensive myocardial necrosis. Death never occurred, as has been mentioned, immediately after the development of this electrocardiographic pattern. A fatal outcome was usually the result of new and severe anginal attacks, followed by different electrocardiographic changes. It is likely that infarction which is indicated by the pattern $T_1 < T_3$ involves only the inner layers of the myocardium. It has been shown that injury of the epicardial portions invariably causes high

take-off of the S-T segment; this does not happen when the subendocardial layers of the heart muscle are injured.[10, 11] Also, the appearance of a W-shaped QRS complex in Lead IV in eight of our cases points to involvement of the inner layers of the myocardium.[12]

The electrocardiographic pattern $T_1 < T_3$ occurs rather frequently. During the last two and a half years, we have observed it in thirty cases in which there was evidence of inadequate nutrition of the heart muscle. It is of great diagnostic value, especially when other electrocardiographic changes indicative of myocardial infarction are absent, as happened in nine of our cases. Case 7 affords a good illustration. Abnormally low voltage of T_1 is not an invariable feature of the pattern $T_1 < T_3$. The latter usually results both from flattening of T_1 and an increase in the voltage of T_3. Occasionally, however, T_1 is of normal amplitude, and it is primarily the increase in voltage of T_3 which causes reversal of the ratio of voltage of T_1 and T_3.

The pattern $T_1 < T_3$ is not specific of myocardial infarction. It may be found in the absence of heart disease when the heart is vertical, and in the presence of pulmonary emphysema. During the last two and a half years, we have observed this in five instances. Especially in cases in which there is a low R_1, the pattern $T_1 < T_3$ should be evaluated cautiously, and a roentgenologic study of the chest be made in order to ascertain whether either of the above-named factors is responsible for the electrocardiographic changes. On the other hand, it should be remembered that myocardial infarction, by itself, may also cause a decrease in the amplitude of R_1. When abnormal position of the heart and pulmonary emphysema have been ruled out, one should consider the possibility of myocardial infarction in older persons, especially in those who give a history of angina pectoris. In young patients, rheumatic heart disease is the most likely cause of the pattern $T_1 < T_3$. During the last two and a half years, we have observed this in five cases. The incidence of the pattern $T_1 < T_3$ in other diseases is almost negligible. During the interval mentioned above, we saw this pattern once with thyrotoxicosis, once in a case of severe anemia, twice with uremia, and in one instance with hypothyroidism.

Examples of the pattern $T_1 < T_3$ are readily available in the literature, especially in the current textbooks on electrocardiography. In Graybiel and White's "Electrocardiography in Practice"[13] we found twelve examples of the pattern $T_1 < T_3$. In five cases (Figs. 103, 105, 121, 208, and 251) the clinical diagnosis was myocardial infarction. In four cases (Figs. 140, 221, 239, and 259) coronary heart disease was diagnosed. In one instance (Fig. 258), the diagnosis was acute and chronic rheumatic heart disease. In another case (Fig. 271) trichinosis was diagnosed. One tracing (Fig. 29), which also presented the pattern $T_1 < T_3$, was attributed to a healthy physician. He was 105 years old, and died one year after the tracing was taken.

In Katz' "Exercises in Electrocardiographic Interpretation"[14] the pattern $T_1 < T_3$ is shown in eight tracings. Two of them (Cases 41 and 51) were from patients with rheumatic heart disease, and two others (Cases 70 and 79) were from patients with congenital heart lesions. In two instances (Cases 42 and 44) myocardial infarction was diagnosed. Of interest are Cases 3 and 63. In discussing Case 3, in which there were upright T waves in all leads, with the pattern $T_1 < T_3$, and with R_4 absent, the author remarked: "The patient, a male, aged 70 years, showed more than his expected disability from his arteriosclerotic heart disease clinically. . . . The record is surprisingly normal in view of the clinical history." In Case 63 there was, in the initial stage of posterior wall infarction, an increase in the amplitude of T_2 and T_3, resulting in a reversed ratio of voltage of T_1 and T_3; later, inversion of T_2 and T_3 was observed. Thus, the pattern $T_1 < T_3$ may exceptionally develop during the acute stage of posterior wall infarction.

Katz' "Electrocardiography"[1] contains eighteen tracings with the pattern $T_1 < T_3$. In two instances (Fig. 76*A* and *B*) the heart was pendulous; in one case (Fig. 202*A*) there was pulmonary emphysema. In six cases (Figs. 110*B*, 128*A*, 132*B*, *C*, and *D*, 134*B* and *C*, 140*B*, and and 143*C* and *D*) the diagnosis was myocardial infarction; in three cases (Figs. 175*A* and *B*, 180*A*, *B*, and *C*, and 195*A*) "progressive coronary insufficiency" was diagnosed. Other examples of the pattern $T_1 < T_3$ included two cases of rheumatic heart disease (Figs. 185*B* and 219*B*), two cases of vitamin deficiency (Figs. 210*B* and 211*B*, *C*, and *D*), and one case of hyperthyroidism (Fig. 205*A*). In two instances (Figs. 71*B* and 73*B*), the clinical data and the diagnosis were not reported.

In a paper, "Delayed Electrocardiographic Changes in Coronary Occlusion,"[15] Strauss presented a case (No. 3) in which there were a flat T_1 and an elevated T_3 a day after a severe anginal attack (Chart 3*C*). The author remarked that the electrocardiographic changes were minimal, and "definitely out of line with the history and findings of a coronary occlusion."

In a paper by Feil[16] we found two tracings (Case 8, Fig. 2*b*, and Case 15, Fig. 3*b*) which presented the pattern $T_1 < T_3$ during "preliminary pain in coronary thrombosis."

In a case reported by Wilson and Johnston,[17] the pattern $T_1 < T_3$ (Case 2, Fig. 1*C*) occurred. The tracing was from a patient who suffered from angina pectoris and had attacks of pain even during rest; one severe attack was brought on by shoveling snow.

Bellet, Kershbaum, and Furst[18] reported a case in which development of the pattern $T_1 < T_3$ was observed after shock treatment (Case 2*B*). Later, T_1, T_2, and T_4 became inverted, and leucocytosis developed. The authors thought that hemorrhage into the ventricular myocardium might have been responsible for the electrocardiographic changes.

CONCLUSIONS

Evidence derived from our own observations and from reports in the literature indicates that the electrocardiographic pattern $T_1 < T_3$ is, in the overwhelming majority of cases, equivalent to the T_1 type of myocardial infarction. This is especially true when the patient is over 40 years of age and gives a history of angina pectoris. In young persons, rheumatic heart disease is the more likely cause. The incidence of the pattern $T_1 < T_3$ in other diseases, such as thyrotoxicosis, uremia, congenital heart disease, vitamin deficiency, and trichinosis, is rare and almost negligible. A vertical position of the heart, in the absence of heart disease, and pulmonary emphysema may also occasionally cause reversal of the ratio of voltage of T_1 and T_3.

SUMMARY

Forty-five cases, in which the electrocardiographic pattern $T_1 < T_3$ occurred in the absence of inversion of T, are reported. In 75 per cent of the cases, clinical and laboratory data furnished dependable evidence of the presence of recent or old myocardial infarction. In the remaining 25 per cent there were symptoms and signs suggestive of coronary arteriosclerosis and ischemic myocardial necrosis. Similar cases are cited from the reports of others.

Under normal conditions T_1 is of greater amplitude than T_3. Reversal of the ratio of voltage is occasionally observed with a vertical position of the heart in the absence of heart disease, and with pulmonary emphysema. In the overwhelming majority of cases, the pattern $T_1 < T_3$ is equivalent to the T_1 pattern of myocardial infarction. It is also occasionally observed in rheumatic heart disease, and in rare cases of congenital heart lesions, thyrotoxicosis, anemia, vitamin deficiency, uremia, and trichinosis.

When the pattern $T_1 < T_3$ occurs in persons over 40 years of age who give a history of angina pectoris, myocardial infarction should be considered first in the diagnosis. The pattern $T_1 < T_3$ may indicate recent or, more often, old myocardial infarction. It is of particular value in the recognition of infarction when other electrocardiographic changes are absent and the tracing appears to be "within normal limits." In young persons, rheumatic heart disease is the most frequent condition underlying the pattern $T_1 < T_3$.

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THE EFFECTS OF VARIOUS SULFONAMIDE DRUGS ON THE ELECTROCARDIOGRAM OF THE DOG

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ALTHOUGH a great many papers have been published concerning the effects of various sulfonamide drugs on liver, central nervous system, kidney, etc., relatively few have dealt with the effect of these drugs on cardiac muscle.

Nelson[1] reports histopathologic changes in the cardiac muscle of rabbits and hens. In a group of twenty-one rabbits to which fatal doses of sulfanilamide had been given, fourteen hearts were examined. All sections were negative, and two on which fat stains were made were fat-free. In a second group of fifteen rabbits which received fatal doses of sulfanilyl sulfanilamide, twelve hearts were examined, and eleven of these were negative. In a group of seventeen hen hearts, however, twelve were negative, two were fat-free, and five showed myocardial damage. Hawkins,[2] reporting on the pharmacologic actions of sulfanilamide, states that it has almost no action on the heart of the frog. Litchfield,[3] who also used sulfanilamide on frog hearts, reported no apparent effect on rate, amplitude, or type of contraction with concentrations below 300 mg. per cent. Using a much higher concentration (800 mg. per cent) on one heart, he found slowing in rate, decrease in amplitude, and rapid cessation of activity. Mendenhall and Shreeve,[4] who also worked with the frog heart, reported that the effect of sulfanilamide (0.25 per cent solution) is stimulation followed by depression. The effect is progressively more depressive as the concentration of sulfanilamide is increased.

On the other hand, Barnes,[5] who studied turtle hearts, reports "the excised auricles of the turtle are chronotropically and inotropically stimulated by 1 per cent sulfanilamide. The oxygen consumption of slices of ventricle of the turtle heart is not affected by 1 per cent sulfanilamide."

Dozzi[6] reports one case of transient nodal rhythm and myocardial damage in man following the use of sulfanilamide. Scheinberg and Ingle[7] also present evidence suggestive of myocardial damage in man. Each of these, however, is a report of a single case, and in one of them[7] there was no record of an electrocardiogram previous to the administration of the drug.

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Recently, French and Weller,[8] in an extensive pathologic study of 238 patients who had been given sulfonamide drugs, reported interstitial myocarditis in 126 cases. They found that a similar condition was produced in the hearts of mice and rats by daily intraperitoneal injections of neoprontosil, sulfanilamide, sodium sulfapyridine, and sodium sulfathiazole.

The present study was undertaken to show the effects of various sulfonamide drugs on the electrocardiogram of the dog. The series includes sixteen dogs. These animals were trained to lie perfectly still (unanesthetized) while the electrocardiogram was being taken. From nine to sixteen control tracings, over a period of two weeks, were taken on each animal before the drug experiments were begun.

All of the drugs were administered intraperitoneally. They were distributed as follows: sodium sulfapyridine, six dogs; sodium sulfathiazole, five dogs; and sodium sulfadiazine, five dogs. Of this group, each drug was used on one dog in a 28-hour experiment (discussed later). The other thirteen experiments were carried out in a series. Each series represented eight to seventeen daily doses, ranging from 0.15 Gm. to 0.2 Gm. per kilo of body weight. These were given on four to five successive days, and rest periods of one week were allowed between series.

During the 28-hour experiment, the concentration of the drug in the blood was ascertained by the method of Bratton and Marshall,[9] using the photoelectric colorimeter. The concentrations attained gave the same toxic effects which have been repeatedly reported in both man and experimental animals, namely, loss of appetite, nausea, vomiting, and kidney involvement. These toxic effects were observed in each case in the weekly series, although blood levels were not routinely ascertained.

Six hundred forty-two tracings (Lead II) were analyzed. These were measured for heart rate and conduction time (P-R interval), and carefully checked for any abnormality of rhythm or conduction.

In several of the animals, an increase in heart rate, with a corresponding decrease in P-R interval, was observed in the tracings taken three to four hours after the administration of the drug. The rate and P-R interval had returned to normal within twenty-four hours. In two dogs, ventricular premature systoles were present in a few tracings. Also, in several dogs, T_2 was inverted. However, this inversion is rather common in dogs, and the form of the wave did not appear altered by the administration of the drug.

Aside from these changes, in no case was there any apparent myocardial damage due to the drug.

In order to reproduce as nearly as possible the conditions in acute infections in which the drug is given in a large initial dose, followed by smaller doses at three- or four-hour intervals, a 28-hour experiment was performed.

Four dogs were used—one control, and one each for sodium sulfapyridine, sodium sulfathiazole, and sodium sulfadiazine.

On each animal, control electrocardiograms (eight to sixteen in number) had been taken during the two weeks preceding the test. On the day of the experiment, at 2 P.M., an electrocardiogram was taken and

blood drawn from the jugular vein for blood sugar, pH, and drug concentration estimations. Drugs were injected immediately after this procedure in each case; 0.2 Gm. per kilo of body weight was the initial dose, followed by 0.1 Gm. per kilo at four-hour intervals, until a total of six doses had been given.

The results of these 28-hour experiments are shown in the tables. Control dog 1 was given sodium sulfadiazine (0.2 Gm. per kilo) daily from April 13 to 17—five doses in all. On April 25, eight days later, she was used as the control for the 28-hour experiment. As can be seen from Table I, there were still traces of sodium sulfadiazine in the blood.

TABLE I

DOG 1 CONTROL

(28-HOUR EXPERIMENT)

PROCEDURE	TIME	DRUG LEVELS IN BLOOD FREE	TOTAL	COMB.	Bl.S.	pH.	H.R.	P-R
Control	2 P.M.	7.8	6.7	0	52	7.34	57	0.130
1	6 P.M.	--	--	--	47	7.30	77	0.120
2	10 P.M.	4.5	4.5	0	51	7.32	--	----
3	2 A.M.	4.1	3.8	0	37	7.28	84	0.116
4	6 A.M.	2.7	2.3	0	36	7.28	64	0.123
5	10 A.M.	2.7	2.4	0	54	7.33	76	0.124
6	2 P.M.	2.3	2.3	0	56	7.28	70	0.124
	29 hours after drug had been discontinued						77	0.120

Bl S.=Blood sugar (Somogyi-Schaffer)
H. R.=Heart rate
P-R=A-V conduction time in seconds

Table II shows the effect of the administration of sodium sulfapyridine. There was a marked increase in heart rate, with a corresponding decrease in P-R interval, as the drug concentration in the blood increased. Twenty-nine hours after the drug had been discontinued, the heart rate fell and the P-R interval increased correspondingly.

TABLE II

DOG 2 SODIUM SULFAPYRIDINE

(28-HOUR EXPERIMENT)

PROCEDURE	TIME	DRUG LEVELS IN BLOOD FREE	TOTAL	COMB.	Bl.S.	pH.	H.R.	P-R
Control	2 P.M.	0.13	0.13	--	75	7.34	86	0.100
1	6 P.M.	21.5	20.5	0	84	7.23	136	0.104
2	10 P.M.	26.6	27.8	1.1	84	7.24	150	0.096
3	2 A.M.	32.4	32.4	0	126	7.22	139	0.096
4	6 A.M.	34.3	35.3	1.0	63	7.28	139	0.096
5	10 A.M.	37.7	38.5	.8	69	7.24	158	0.099
6	2 P.M.	40.3	41.4	1.1	72	7.24	176	0.096
	29 hours after drug had been discontinued						77	0.124

Table III, which depicts the effects of the administration of sodium sulfadiazine, also shows an increase in heart rate, but not as marked as after sodium sulfapyridine. Table IV, which summarizes the sulfathiazole effects, also shows a marked increase in heart rate, with a cor-

TABLE III

DOG 3 SODIUM SULFADIAZINE

(28-HOUR EXPERIMENT)

PROCEDURE	TIME	DRUG LEVELS IN BLOOD FREE	TOTAL	COMB.	Bl.S.	pH.	H.R.	P-R
Control	2 P.M.	0	0	0	55	7.30	65	0.116
1	6 P.M.	27.6	26.1	0	47	---	94	0.120
2	10 P.M.	36.0	38.5	2.5	44	7.29	90	0.124
3	2 A.M.	51.0	54.5	3.5	41	7.28	79	0.120
4	6 A.M.	62.8	69.0	6.2	37	7.27	83	0.118
5	10 A.M.	76.6	82.1	5.5	41	7.22	70	0.120
6	2 P.M.	87.6	96.5	6.9	45	7.21	74	0.124
48 hours after drug had been discontinued							86	0.110

TABLE IV

DOG 4 SODIUM SULFATHIAZOLE

(28-HOUR EXPERIMENT)

PROCEDURE	TIME	DRUG LEVELS IN BLOOD FREE	TOTAL	COMB.	Bl.S.	pH.	H.R.	P-R
Control	2 P.M.	0	0	0	65	7.34	80	0.124
1	6 P.M.	12.1	12.2	0.1	57	7.35	86	0.124
2	10 P.M.	10.2	10.4	0.2	57	7.34	94	0.120
3	2 A.M.	12.3	13.8	1.5	72	7.32	109	0.116
4	6 A.M.	12.9	13.6	0.7	58	7.32	107	0.114
5	10 A.M.	11.0	11.1	0.1	59	7.32	92	0.124
6	2 P.M.	11.8	13.0	1.2	71	7.31	78	0.116
29 hours after drug had been discontinued							102	0.112

respondingly decreased P-R interval, as the drug concentration in the blood increased. Twenty-nine hours after the drug had been discontinued, the heart rate was still above the control. This increase had disappeared when a tracing was taken four days later.

All tracings obtained during the 28-hour experiment were carefully checked for abnormalities of rhythm and conduction. The results confirmed those obtained in the series experiments. In no case in this study was any myocardial damage found which could be attributed to the use of the drug.

Except for two dogs which died of distemper during the year, the others remained in apparently splendid physical condition.

SUMMARY

Experiments were performed on sixteen dogs to show the effects of various sulfonamide drugs. Sodium sulfapyridine, sodium sulfadiazine, and sodium sulfathiazole were used.

Six hundred forty-two tracings (Lead II) were taken, and measured for heart rate and P-R interval. All were carefully checked for abnormalities of rhythm or conduction.

No evidence of myocardial damage which could be attributed to the drug was found in this study.

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THE BASAL WEIGHT LEVEL IN THE TREATMENT OF CONGESTIVE HEART FAILURE

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THE foremost question in the mind of the physician when dealing with congestive heart failure is: "How can I attain and then maintain a completely edema-free state for my patient?" This, of course, is the goal toward which diuretic therapy should be meticulously directed. Previous reports[1, 2] have emphasized the value of a graphic record of the daily weight of the patient in the treatment of congestive heart failure. Its advantages have been pointed out in those papers and will not be reviewed here.

It occurred to us, however, that an accurate daily weight record could provide the instrument by which the physician would be certain to know when his patient had attained the ideal state. As will be shown, it is possible to remove all of the edema from the extracellular tissue spaces by the intensive use of mercurial diuretics. This end result is designated as the "basal weight level." It should be pointed out that this term does not represent merely the disappearance of edema in the usual sense, but actually describes a state, as indicated by the weight chart, in which no additional fluid can be driven out of the body by the further use of diuretics.

We present here a simplified procedure which has been used to bring about and maintain this "basal weight level" in seventeen patients who have been followed continuously for periods varying from 76 to 977 days (Table I).

At present, all except five, who have died, remain under our observation. Another woman, who recently developed congestive heart failure of hypertensive origin, was also treated in this way, and her weight chart is reproduced in Chart I. Although she is not included in the group of seventeen cases which were studied at greater length, her chart shows a characteristic type of response, and further signifies the ready applicability of this system of therapy.

The procedure which is used in these cases may be described as follows: The patient, in the usual hospital gown, is weighed daily, before breakfast, and the weight is recorded on the chart (Chart I). Fluids are not restricted. Digitalis is employed in the accepted dosage as the need arises in each case. Ammonium chloride is given in the usual dose of 90 grams (6 Gm.) daily. A mercurial diuretic is administered on alternate days. It is preferred that 2 c.c., together with

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an equal amount of 1 to 2 per cent procaine hydrochloride solution, be given intramuscularly into the buttock in the morning (preceded at the outset by a test dose of 0.5 c.c.).* Usually a more or less rapid weight loss results, as can be seen on the chart (Chart I), until a plateau develops in the curve. From that point, the height of the curve remains unchanged, although the mercurials continue to be injected on alternate days as before.

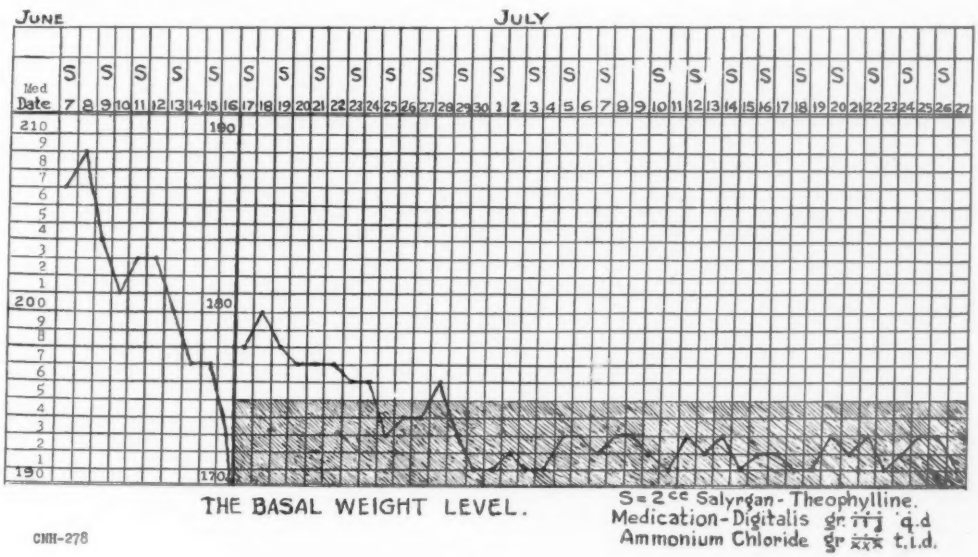

Chart I.

It is arbitrarily considered that the "basal weight level" has been reached when the daily weight changes do not exceed a 5-pound range for a period of fourteen consecutive days. (This area can be conveniently shaded in colored crayon.) At this juncture the mercurial is discontinued until further need for it is indicated on the chart by any rise in the weight above the "basal weight level." The frequency with which the mercurial injections are required seems to be somewhat proportional to the severity of the underlying heart disease. For example, in some cases the injection must be given as often as every other day for an indefinite period in order to maintain the patient at his "basal weight level," whereas, in others, the patient's weight is so constant that it may be represented by a straight line. It has been the policy in the latter group to utilize a so-called "trial dose" in order to avoid an undesirable accumulation of fluid.

*In "A Review of the Toxic Manifestations of Mercurial Diuretics in Man," DeGraff and Nadler[3] comment that "in the reported cases of sudden death from mercurial injection *no deaths* have been reported from the administration of the mercurial diuretics intramuscularly or by rectum." The intramuscular administration of the mercurials has been used exclusively in our series, without any untoward reactions. Furthermore, the diuresis after such injections is quite satisfactory, and probably more prolonged than when the intravenous method is employed.

TABLE I

OBSERVATIONS DURING FREQUENT ADMINISTRATION OF MERCURIALS

PATIENT	DURATION OF TREATMENT	MERCURIALS	ADMISSION URINE				PRESENT URINE				AUTOPSY
			CASTS	ALB.	W.B.C.	R.B.C.	CASTS	ALB.	W.B.C.	R.B.C.	
1. D. S. (D.)	155 days	48 injections	0	0	0	0	0	0	0	0	No tubular damage
2. P. M. (D.)	321 days	90 injections	0	3+	0	0	0	2+	0	0	Severe cloudy swelling
3. M. B. (D.) (F.)	78 days	32 injections	0	2+	occ.	0	0	4+	few	0	No tubular damage
4. J. G. (D.)	158 days	28 injections	0	0	0	0	0	0	0	0	No autopsy
5. J. M. (D.)	424 days	41 injections	0	0	rare	0	0	0	0	0	No tubular damage
6. W. D.	555 days	131 injections	rare-gran.	3+	rare	0	0	0	0	0	
7. F. F. (F.)	977 days	214 injections	0	1+	0	0	0	2+	0	0	
8. L. M.	397 days	107 injections	some finely gran. & fatty	4+	0	0	0	3+	0	0	
9. J. N.	418 days	11 injections	0	3+	loaded	0	0	2+	occ.	0	
10. M. R. (F.)	480 days	129 injections	0	0	1-2/HPF	0	0	0	10-20/HPF	0	
11. F. S.	340 days	22 injections	0	0	0	0	0	0	0	0	
12. B. S.	584 days	73 injections	0	3+	0	0	0	0	0	0	
13. A. S.	412 days	49 injections	0	0	4-8/HPF	0	0	0	0	0	
14. H. S.	294 days	67 injections	0	0	0	0	0	0	0	0	
15. R. M. (F.)	659 days	212 injections	0	4+	3-10/HPF	0	hyal.	0	3-4 occ.	0	
16. J. D.	76 days	32 injections	occ.	2+	occ.	occ.	0	0	0	0	
17. J. P.	381 days	102 injections	0	0	rare	0	0	0	occ.	0	
Total	6,709 days	1,388 injections									
Average	394.65 days	81.64 injections									

(D.) = Deceased
(F.) = Female
occ. = Occasional
HPF = High-Power Field
hyal. = Hyaline
gran. = Granular

It is to be emphasized that approximately 10 pounds of fluid can accumulate in the body before even minimal traces of edema, e.g., pretibial edema, can be demonstrated clinically, but the present method detects and eliminates this undesirable accumulation of latent fluid well within the 5-pound limit of the "basal weight level" (see Chart I). It is unnecessary to wait for the reappearance of gross edema as an indication for the next mercurial injection, and, therefore, edema as such does not exist under this regime. Any system of therapy which embraces diuretics in the management of congestive cardiac failure and employs the clinical detection of edema as a guide must take into account the continuous presence of latent fluid in the tissues. On the other hand, the patient at the "basal weight level" is maintained at all times in an edema-free state.

It is to be noted that this method employs at the outset a more frequent rate of administration than is customary with the intravenous route, but we feel that this is the very reason for its success, because a more *continuous* diuresis is established.

We have been keenly aware of the possibility that various untoward effects might result from such an intensive use of mercurials. Usually, renal and gastrointestinal disturbances are the reactions which are associated with the use of mercury in toxic doses.

DeGraff and Nadler,[3] in describing changes produced in the kidney by mercurial diuretics, emphasize the degeneration of the tubular epithelium. They state that the abnormalities in the urine produced by irritation from mercurial diuretics appear in the following order: (1) casts, (2) albumin, (3) leucocytes, and (4) erythrocytes. Several instances of mild renal irritation from mercurials have been reported by Sprague and Graybiel,[4] Herrmann and Decherd,[5] Klinghoffer,[6] Brown and Englebach,[7] and others. In a series of thirty autopsies on patients who received salyrgan during life, Tarr and Jacobson[8] found only one patient with a renal lesion suggestive of mercurial intoxication. In our series of five deaths (Table I, Patients 1 to 5), four autopsies were performed. No indication of tubular damage was found in any case, although in one there was evidence of cloudy swelling of the kidneys. We have focused our attention on the urine in every case, and reference to Table I reveals that, over a long period of observation, during which as many as 200 or more injections were given, urinalysis in most cases actually showed a striking improvement, rather than the development of renal damage. This improvement is more than likely due to the disappearance of the passive congestion in the kidneys. No gastrointestinal symptoms, such as stomatitis, salivation, and hemorrhagic colitis, occurred in our series.

In general, we are in agreement with Wiseman,[9] Maxwell, Scott, and Harvey,[10] Dixson,[11] Levine,[12] and Fineberg[13] on the low toxicity of the mercurial diuretics. Hence, with our method, there has been no cause

to fear even the most frequent use of mercurials that is necessary to bring patients with severe congestive cardiac failure to the "basal weight level."

SUMMARY

1. In a series of seventeen cases of congestive heart failure which were followed over varying periods of time (76 to 977 days), we produced and maintained a completely edema-free state which we have termed the "basal weight level."

2. The simple procedure which is employed in gaining this end is described and exemplified by the actual weight chart in a typical case.

3. The advantages of a system whereby the cardiac patient is at all times assured of freedom from edema are emphasized.

4. No untoward reactions attributable to the frequent use of the mercurials were noted with this method, either in the urine or at post-mortem examination.

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BICUSPID AORTIC VALVES AND BACTERIAL ENDOCARDITIS

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CONGENITAL cardiac defects, especially a bicuspid aortic valve, have generally been assigned an important role in the pathogenesis of bacterial endocarditis.[1-5] Such defects are considered to be susceptible to the development of endocarditis.

Among fifty adult hearts with bicuspid aortic valves, there were eight with superimposed bacterial endocarditis. Analysis was undertaken to ascertain the relation of the bicuspid lesions to the bacterial disease. The results do not support the view that a congenitally bicuspid aortic valve is a significant precursor of bacterial endocarditis.

MATERIALS AND METHODS

The material consisted of eight adult hearts, all with a bicuspid aortic valve which was the seat of bacterial endocarditis. The hearts were studied grossly and microscopically to ascertain (1) the type of bicuspid aortic valve, (2) the nature and distribution of the bacterial disease, and (3) whether or not there were stigmas of rheumatic fever.

The type of bicuspid lesion was established by study of the raphe, or ridge, behind the conjoined aortic cusp. The gross appearance of each raphe was noted, and then transverse or longitudinal microscopic sections were obtained. Serial sections were made in several instances. The preparations were stained with hematoxylin and eosin, Weigert's method for elastic tissue, or the combined Weigert and Van Gieson methods for elastic and fibrous tissue.

The bacterial lesions were subdivided into acute bacterial endocarditis and endocarditis lenta (subacute bacterial), depending on their gross and microscopic character. An important morphologic criterion of endocarditis lenta is the presence of organization tissue at the base of the vegetations. The valvular distribution of the lesions was noted in each heart.

To detect rheumatic stigmas, the hearts were subjected to microscopic study of blocks made according to the method of Gross, Antopol, and Sachs,[6] and numerous additional sections were made from the valves.

Only unequivocal stigmas of rheumatic heart disease were accepted. Grossly, such stigmas include thickening, shortening, and commissural fusion of the valves, especially the mitral and tricuspid, thickening and adhesion of the chordae tendineae, nodular thickening and wrinkling of the left atrial endocardium, and fibrous pericardial adhesions. Characteristic microscopic lesions consist of vascularity, exudate, and fibrosis in the attachment and free portion of the valves, involving especially the auricularis layer of the mitral and tricuspid valves and the ventricularis layer of the semilunar valves, vascularity and reduplication of the elastica of the endocardium of the left atrium and the subaortic angle, and Aschoff nodules in the myocardium.

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RESULTS

Type of Bicuspid Aortic Valve.—Seven of the bicuspid aortic valves were acquired and one was congenital.

Of the seven acquired lesions, the raphe was situated at commissure A* in six, and at commissure B in one. Grossly, the raphes were all similar in appearance. Each consisted of a firm ridge of fibrous tissue, usually wider distally than proximally, and passing obliquely in the sinus of Valsalva from the proximal origin at the upper commissural level to insert distally into the conjoined cusp. The insertion was in the basal third of the conjoined cusp in all but one instance, in which it was located in the outer third. The raphes were symmetrical in six cases, and slightly irregular or distorted in two cases because of calcific deposit. None of the lesions revealed a fissure in the outer surface.

Microscopically, the raphes were composed of dense, hyalinized, fibrous tissue and contained little or no elastica. In longitudinal sections, vascularity and sometimes exudate were present in the ventricularis layer along the base of the raphe, especially in the distal segment, and were usually prominent in the region of attachment of the valve and the subaortic angle. In transverse sections, vessels were seen in the lateral or basal regions, corresponding to the attachment of the fused cusps. In every case the junction of aortic media and annulus fibrosus occurred behind the proximal extremity of the raphe, and the annulus was situated anterior to the media.†

In the congenitally bicuspid aortic valve, the ridge was situated at commissure A. It consisted grossly of a long, narrow, hemicylindric elevation of aorta, of uniform width and depth, projecting only slightly into the sinus of Valsalva, and directed in the long axis of the aorta. In the distal half, the surface revealed a longitudinal fissure. Microscopically, the ridge was composed almost entirely of elastic tissue, whorled centrally, and continuous laterally with that of the aortic media. The elastica terminated in the distal part of the ridge by overlapping the annulus fibrosus both anteriorly and posteriorly; the posterior overlap descended to a lower level than the anterior. No inflammatory changes were observed in the ridge.

Lesions of Bacterial Endocarditis.—All eight bicuspid aortic valves were the seat of superimposed bacterial endocarditis. The lesions were acute bacterial in four cases and endocarditis lenta in four cases. The gross and microscopic appearance of the vegetations was characteristic. In six cases the bacterial disease was confined to the aortic valve, whereas in two others, in both of which the bicuspid aortic valve was acquired, the mitral leaflets also showed vegetations.

*The following nomenclature of the aortic valve is used: the aortic cusps are designated according to the situation of the coronary ostia, as the left, the right, and the noncoronary cusps.

The left-right commissure is referred to as commissure A, the right-noncoronary commissure as commissure B, and the left-noncoronary commissure as commissure C.

†When the annulus is anterior to (or in front of) the aortic wedge, it is separated by the latter from the pericardium. If the annulus be posterior to (or behind) the wedge, it is in contact with the pericardium.

Lesions of Rheumatic Fever.—In every case, including the congenital bicuspid lesion, the aortic valve showed gross changes indicative of rheumatic disease. The cusps were the seat of slight to marked thickening, especially along the line of closure. In the conjoined cusps, thickening was generally prominent in the region bordering on the commissural raphe. Calcific nodules were present in slight or moderate amount in five cases, either in the substance of the cusps or projecting into the sinuses of Valsalva. Inrolling of the free margins was observed in two instances. In only one case, that of an acquired bicuspid aortic valve, with the raphe at the commissure A, was there additional commissural fusion, namely, a submarginal adhesion at commissure B.

Microscopically, the aortic cusps generally showed lesions characteristic of rheumatic fever, such as fibrosis, vascularity of the attachment and free portion, and calcific deposit.

Gross rheumatic stigmas other than those of the aortic valve were observed in six of the eight hearts. Chronic, nondeforming mitral valvulitis was present in six cases, nondeforming tricuspid valvulitis in two instances, nodular thickening of the left atrium in two instances, and pericardial adhesions in one case. In two hearts with acquired bicuspid aortic valves which were the seat of acute bacterial endocarditis, no conclusive, gross, rheumatic stigmas were found outside the aortic valve. In the heart with a congenitally bicuspid aortic valve, there was a nondeforming rheumatic lesion of the mitral valve.

Seven of the eight hearts revealed definite microscopic evidence of rheumatic disease in situations other than the aortic valve. There were lesions of the mitral valve in seven cases, of the left atrium in three cases, and the tricuspid valve in three instances. Aschoff nodules were seen in the left ventricle in one case. In one of the two hearts which showed isolated rheumatic aortic valvulitis in the gross, the microscopic stigmas of rheumatic fever were also limited to the aortic valve. In the heart with a congenitally bicuspid aortic valve, rheumatic stigmas were present in the mitral valve and left atrium.

COMMENT

Early writers on the subject of bicuspid aortic valve did not distinguish clearly between congenital and acquired types.[7-9] Although the possibility of acquired origin was admitted, it was generally thought that most of the lesions were congenital. Osler[9] held this view on the basis of gross criteria which are now known to be inadequate.[10, 11] The frequent association of a bicuspid aortic valve with bacterial endocarditis was attributed to the assumption that the congenitally defective tissue is susceptible to bacterial invasion.

Lewis and Grant[1] were the first to distinguish morphologically between congenital and acquired bicuspid aortic valves. They directed their attention especially to the congenital ridge behind the conjoined cusp. This was studied in its entirety with serial transverse micro-

scopic sections stained for elastic tissue. It was found to consist chiefly of elastic lamellae which were derived from the adjacent aorta and passed across the ridge in symmetrical manner. In the central portion there was a peculiar whorling pattern. In addition, the elastica extended down almost to the distal end of the ridge, and its terminal portion was frequently anterior to the annulus fibrosus.

In contrast, the ridge, or raphe, behind the conjoined cusp of the acquired bicuspid aortic valve revealed a structure derived from that of two fused cusps. Residua of chronic inflammation could be observed. The raphe contained no elastica. The junction of aortic media and annulus fibrosus occurred in the proximal extremity of the raphe, and the usual commissural relation was maintained, namely, the annulus was superficial to the elastica.

Lewis and Grant's material comprised a total of thirteen congenitally bicuspid aortic valves. Of these, eight occurred among a group of thirty-one consecutive adult hearts with endocarditis lenta. Thus, the authors stressed not only the frequency of a congenitally bicuspid aortic valve, but also its importance as a predisposing cause of bacterial endocarditis. The latter was explained by the theory that the congenital deformity constitutes a focus which is favorable for the implantation of bacteria. The authors estimated that 23 per cent of all persons with congenitally bicuspid aortic valves would develop endocarditis lenta after reaching adult life.

The validity of Lewis and Grant's work, especially with respect to the specific morphology of the congenital ridge, was later questioned by Gross.[10] Such supposedly congenital characteristics as whorling and continuity of the elastica, and alteration of the terminal aortic wedge insertion into the annulus fibrosus, were attributed by him to an inflammatory origin. Gross maintained that practically all bicuspid aortic valves in adults are acquired lesions, and are produced in most instances by rheumatic fever. This etiological factor readily explained their frequent association with superimposed bacterial disease.

Recently, Koletsky[11] studied the morphology of bicuspid aortic valves in newborn babies and infants. Here the lesions were undoubtedly congenital in origin. The microscopic structure of the congenital ridge was studied by means of serial transverse and longitudinal sections. Thus, an adequate means was provided for ascertaining the nature of bicuspid aortic valves in adults. In the latter, the distinction between congenital and acquired lesions was found to depend solely on structural differences between the congenital ridge and the acquired commissural raphe.[11, 12]

The gross appearance of the congenital ridge is characteristic. It consists of a long, narrow, barlike elevation of the aorta, symmetrical, of uniform width and depth, and directed in the long axis of the aorta. The microscopic appearance is similar to that described by Lewis and Grant, except for the junction of aortic media and annulus fibrosus in

the distal part of the ridge. This junction generally occurs in an inverted V-shaped manner, with the aortic wedge overlapping the annulus both anteriorly and posteriorly, and with the posterior overlap usually descending to a lower level than the anterior. Occasionally the junction is beveled, and the elastic wedge is either entirely anterior or posterior to the annulus.

The raphe of acquired bicuspid aortic valves consists of a firm oblique ridge of connective tissue, usually wider distally than proximally, often symmetrical, but sometimes irregular or distorted, especially when calcific deposit is present. Occasionally the raphe is markedly depressed, and occupies a horizontal position at the bottom of the sinus of Valsalva.[13] The microscopic structure is distinctive. The raphe is composed of dense hyalinized fibrous tissue, may or may not show calcific deposit, and has practically no elastica. Vascularity and exudate are observed, especially in the distal and basal portions. The junction between annulus fibrosus and aortic media occurs at the proximal origin of the raphe, where the media terminates posterior to the annulus.

The original review of protocol records at the Institute of Pathology revealed only eight acquired bicuspid aortic valves in 3,500 consecutive autopsies.[12] Since then, further experience has shown that the acquired lesion is much more common than this figure would indicate. Moreover, in adults it is considerably more frequent than the congenitally bicuspid valve. For example, in approximately the last three years there have been twelve acquired lesions in adults, as compared to one adult congenital lesion in 1,200 consecutive autopsies. In the past, instances of bicuspid aortic valve were undoubtedly overlooked.

Our present figures on bicuspid aortic valves are as follows. A total of fifty bicuspid aortic valves in adults, collected from the autopsy material of University Hospitals and several other Cleveland Hospitals, have been studied. The lesions were divided into acquired and congenital types, according to the criteria enumerated. Forty of the bicuspid aortic valves were acquired and ten were congenital. Of the latter, five were of simple type, i.e., with two normal cusps and no congenital ridge, whereas five revealed a conjoined cusp subdivided by a congenital ridge.

Thus, the great majority of bicuspid aortic valves in adults, in our experience so far, are acquired; a small number are congenital in origin. The former conclusion coincides rather closely with the observations of Gross. His suggestions, however, that congenitally bicuspid aortic valves are confined to children, and that the criteria for their recognition are invalid, are not acceptable. Gross's study was probably handicapped by absence in his material of examples of congenitally bicuspid aortic valves in infants or children. Possibly, however, no congenital lesions were present among the sixteen adult bicuspid aortic valves which he described.

To support the view that congenitally bicuspid aortic valves did not occur in adults, Gross pointed out that, in the adult, bicuspid aortic valves differ from those of children in whom the lesion is definitely congenital. For example, the aortic cusps are thin and delicate in children and thickened in the adult lesion. Moreover, other cardiac anomalies generally accompany the bicuspid valve in children and are absent in adults.

These arguments are valid only in a general way. Isolated congenitally bicuspid aortic valves have been observed in infants, as well as adult lesions both with and without other anomalies. Absence of other anomalies does not preclude a congenital origin for a bicuspid aortic valve, any more than their presence necessarily indicates that the bicuspid valve is congenital. Thus, a heart with a congenital deformity may be the seat of superimposed rheumatic disease, with acquired bicuspid aortic valve. Moreover, our study includes instances of congenitally bicuspid aortic valves with thick cusps in infants, and adult lesions with delicate cusps.

Lewis and Grant's view regarding the high incidence of a congenitally bicuspid aortic valve among patients with bacterial endocarditis has not been confirmed up to the present time. Their experience in this matter is contrary to ours. The difference is puzzling in view of the fact that Lewis and Grant used valid microscopic criteria to identify the congenital lesion. A critical review of their material, however, indicates that in a few cases the morphologic requirements for the congenital ridge appear not to have been adequately fulfilled, and that in a few others the interpretation is open to question. Thus, it is possible that some lesions designated as congenital were actually acquired.

Gross thought that most acquired bicuspid aortic valves are due to rheumatic fever, and a small number to degenerative lesions, such as Mönckeberg's sclerosis. Our studies, including those of Karsner and Koletsky,[14] indicate that the lesions are solely inflammatory, and, in all probability, are produced by rheumatic disease. The evidence in favor of a rheumatic etiology is reasonably conclusive. The raphes of the conjoined cusps differ in no appreciable way, grossly or microscopically, from the commissural raphes of rheumatic aortic valves without bicuspid deformity. The pathologic changes in the aortic cusps, with respect to fibrosis, vascularity, calcific deposit, and elastic reduplications are morphologically indistinguishable from those which occur in rheumatic fever. Moreover, hearts with acquired bicuspid aortic valves generally show conclusive stigmas of rheumatic disease in regions other than the aortic valve. These stigmas are of both gross and microscopic nature, may be distributed focally or widely in the heart, and are most frequent in the mitral and tricuspid valves.

Some data are available in the literature to indicate the frequency of bicuspid aortic valves at autopsy in cases of bacterial endocarditis.

On the basis of Lewis and Grant's work, the authors generally assume, without morphologic study, that the bicuspid lesions are congenital. Starling[15] found four bicuspid aortic valves among thirteen cases of endocarditis lenta. Thayer[16] reported three bicuspid lesions among twenty hearts with acute streptococcal bacterial endocarditis involving the aortic valve, although there were no such lesions in twenty-six similar cases of subacute type. Fulton and Levine[17] observed two bicuspid aortic valves among thirty hearts with subacute bacterial endocarditis. In twenty-eight cases of subacute bacterial endocarditis in patients over 40 years of age, Bayles and Lewis[18] found three bicuspid aortic valves (11 per cent). Braunstein and Townsend[19] reported seven bicuspid lesions among fifty-eight cases of bacterial endocarditis; that they regarded the lesions as congenital is not stated.

Such data indicate that bicuspid aortic valves form a distinct type of underlying valvular defect in bacterial endocarditis. The lesion occurs in 6 to 12 per cent of cases of bacterial endocarditis. No adequate distinction between acquired and congenital lesions has been made, however, and no information offered regarding the presence of rheumatic fever, so that the importance of each type of bicuspid aortic valve in relation to the bacterial disease cannot be ascertained. That all the bicuspid lesions were congenital is doubtful.

The present study lends no support to the view that a congenitally bicuspid aortic valve is a significant precursor of bacterial endocarditis. It indicates that most bicuspid aortic valves in adults are acquired, and, in this respect, confirms the observations of Gross. Congenitally bicuspid aortic valves in infants and children are apparently not susceptible to bacterial disease. Of fourteen such lesions studied by the author, none showed superimposed bacterial endocarditis. The rheumatic nature of acquired bicuspid aortic valves readily explains the frequency of superimposed bacterial infection. In general, no congenital valvular defect can be considered as having led to the development of bacterial endocarditis until the presence of rheumatic disease has been excluded.

Consideration was given to the possibility that the bicuspid lesion, per se, apart from, or in addition to, the underlying rheumatic disease, might predispose to bacterial endocarditis. This was suggested by the fact that, in six of the eight cases, the bacterial disease was confined to the aortic valve. The problem was approached statistically. There were seven cases of bacterial endocarditis among forty acquired bicuspid aortic valves, an incidence of 17 per cent. In comparison, the general incidence of bacterial disease among rheumatic hearts was 12 per cent, i.e., 60 cases among 475 rheumatic hearts. However, among 100 unselected rheumatic aortic valves, with deformity comparable to the bicuspid lesion, there were fourteen cases of bacterial endocarditis

(14 per cent). The differences between these figures are too small to offer any clear-cut indication that the bicuspid deformity itself predisposes to bacterial disease.

SUMMARY AND CONCLUSIONS

Eight hearts with bicuspid aortic valves and superimposed bacterial endocarditis are described. The bacterial disease was acute in four cases and subacute in four cases. Seven of the bicuspid lesions were acquired, and one was congenital. Every heart showed definite stigmas of rheumatic fever. It is concluded that the bacterial lesions in each case were engrafted on the rheumatic disease.

Most bicuspid aortic valves in adults are acquired lesions produced by rheumatic fever. The latter, rather than the bicuspid state, predisposes these valves to the development of superimposed bacterial endocarditis.

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A TILTING BALLISTOCARDIOGRAPH

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IN ORDER to facilitate the use of the ballistocardiograph[1] in any position, it was desired to incorporate one within a tilting table. Such an arrangement would allow ballistocardiograms to be made immediately after changes in position, requiring a minimum of effort and cooperation on the part of the subject.

The chief difficulty encountered was the arrangement of a system for recording the motion of the ballistocardiograph in any position. This was overcome by means of a flexible lead tube attached to a Hamilton optical manometer. An additional advantage of this method was found to be the ease with which the ballistocardiogram could be recorded simultaneously on the same moving film with other physiologic measurements.

DESCRIPTION OF THE APPARATUS (FIG. 1)

A light (22 pound), but rigid, bed was constructed,* using ½ inch 5-ply wood for the top, ½ inch board for longitudinal trusses, and cast aluminum brackets for the end supports. To the latter, at the four corners of the bed, were bolted the spring clamps which held vertical flat springs of tempered tool steel, 1/16 by ½ inch by 3 inches. The upper ends of these four springs, in turn, were held in spring clamps bolted to the frame (4 inch channel) of the tilting table. The axle of the tilting table rested in bronze bearings upon the supporting frame, which was so constructed as to allow a tilt of 75° in either direction. Into one end of the axle a hole was drilled and tapped to take the fitting of the lead tube of the Hamilton manometer. The hole was extended 6 inches into the axle, then around a right angle turn to emerge from the axle under the bed. This opening was tapped to fit a compressible copper bellows, the other end of which was fixed to a crossbar running between the middle and outside wood trusses. Thus, any motion of the bed in relation to the axle caused a compression or extension of the bellows. The free stem of the bellows was drilled and tapped to take a needle valve, which allowed the bellows, the hole in the axle, the lead tubing, and the Hamilton manometer to be filled completely with a noncorrosive fluid† from a reservoir attached by rubber tubing to the side cock of the Hamilton manometer. The Hamilton manometer was then placed in an optical beam for recording.

When not in use, the ballistocardiograph bed was fixed in place within the tilting table frame by a screw at the end of the frame. The side cock on the Hamilton manometer was always left open to the reservoir until a record was ready to be made. This avoided undue motion and strain of the diaphragm in the head of the manometer.

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*By C. E. Clarke & Company, 1934 Revere Beach Parkway, Everett, Mass.

†Dupont "Zerex."

When the tilting table was set in any desired position, indicated by a graduated scale attached to the frame at the end of the axle, it could be rigidly clamped in that position by screwing tight the lock lever at the side of the frame. Then the fixing screw at the end of the frame was released to allow the ballistocardiograph bed to move. The side cock on the Hamilton manometer was closed, and the apparatus was ready to record the motions of the ballistocardiograph imparted to the bellows and, thence, to the Hamilton manometer.

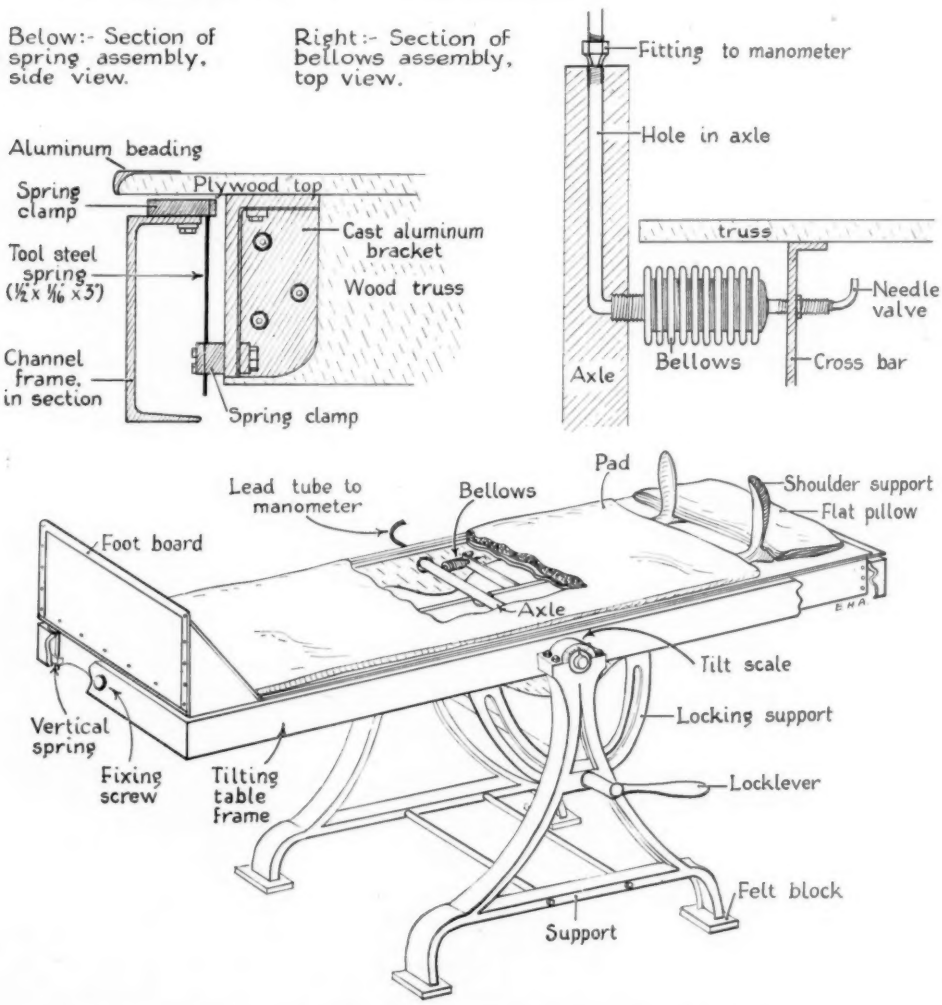

Fig. 1.—Diagram of the tilting ballistocardiograph. For description, see text.

Before changing the position of the table, the side cock to the Hamilton manometer was opened. Opening this cock to the reservoir brought the recording beam to rest at its base line. The bed was equipped with a footboard, and with adjustable shoulder supports to keep the subject from sliding when tilted. The machine was calibrated in any position by loading the bed with sandbags of about the same weight as the subject, and exerting a 500-gram pull on it in either

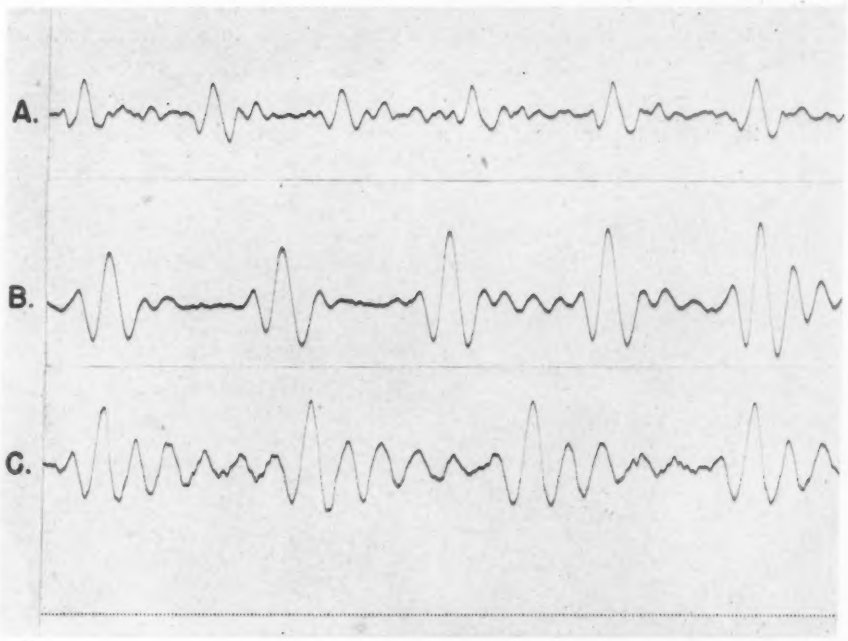

Fig. 2.—Normal ballistocardiograms in different positions. *A*, Upright 75°; *B*, horizontal; *C*, head down 20°.

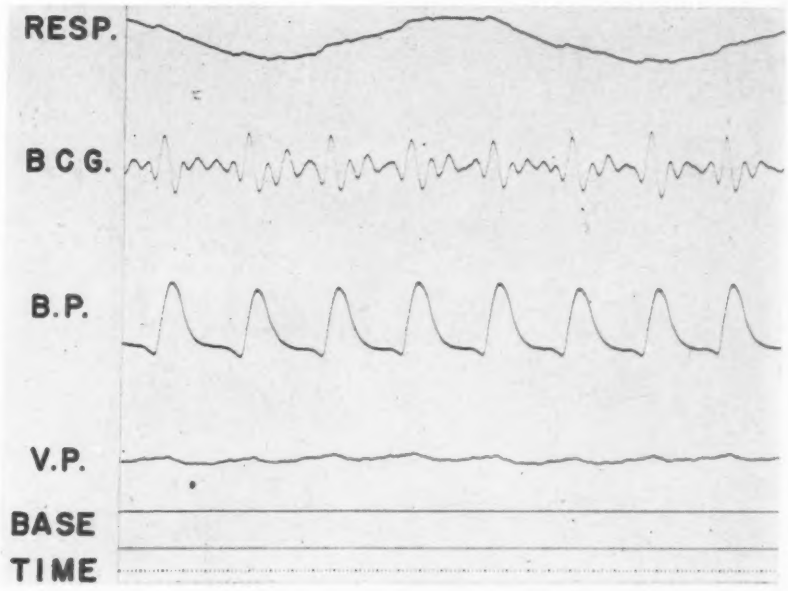

Fig. 3.—Optical record of respiration (inspiration down), ballistocardiogram (horizontal position), arterial pressure (Hamilton method), and venous pressure (Hamilton method) in a normal subject.

longitudinal direction. This was done by suspending a 500-gram weight across a pulley by a thread leading longitudinally to a pin set in the middle truss of the bed.

RESULTS

Fig. 2 shows typical ballistocardiograms taken in three different positions. Records in the horizontal positions have been uniformly satisfactory, but in the steeply tilted positions have often been confused by muscular tremors of the subject. Fig. 3 shows a number of different physiologic measurements recorded simultaneously with the ballistocardiogram. The apparatus has proved most useful in detecting quick or fleeting changes in cardiac function after alterations in position or other experimental conditions. It should also facilitate the study of patients with orthopnea, shock, or other abnormalities which demand a certain position.

SUMMARY

A ballistocardiograph was combined with a tilting table to allow ballistocardiograms to be made readily in any position of the subject.

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COMPARISON OF THE VALUE OF THE WELTMANN REACTION AND THE ERYTHROCYTE SEDIMENTATION RATE IN PATIENTS WITH RHEUMATIC HEART DISEASE

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THIS report is concerned with an analysis of the Weltmann serum coagulation test in a group of patients who had recently had rheumatic fever, and a comparison of the value of this test with the erythrocyte sedimentation rate. We were particularly interested in the problem of whether the development of rheumatic valvular lesions is related to the severity of the original attack of acute rheumatic fever, or to subsequent recurrences of rheumatic activity which are not easily detected by ordinary methods, i.e., "subclinical rheumatic activity." It was thought that variations in the coagulation band, as ascertained by the Weltmann reaction, might occur during periods of occult rheumatic activity, and that it would be informative to evaluate the usefulness of this test in such a group of patients.

The clinical course of rheumatic fever in eighty patients has been carefully observed during the past two years in an attempt to follow the gradual development of valvular heart disease. The patients were seen in the Cardiac Clinic and on the wards of The Johns Hopkins Hospital. Sixty patients had had acute rheumatic fever one or more times during the four years preceding this study. Signs of early mitral stenosis and insufficiency were present in seventeen, and twenty-five patients had marked rheumatic valvular lesions with cardiac enlargement. There were three patients with subacute bacterial endocarditis, one of whom died during the period of observations, and two of whom had apparently recovered after sulfonamide therapy just before they came into this group. Thirty-six patients had no signs of rheumatic heart disease and were under observation since their last attacks of acute rheumatic fever.

The patients were ambulatory, except for two patients during attacks of acute rheumatic fever and polyarthritis, and for some of the others during occasional nonrheumatic illnesses. The ages of the patients ranged from 8 to 40 years, with the greatest frequency around 18 to 20 and 35 years of age. They were seen at regular intervals during the period of study, and were carefully questioned and examined at each visit. Among the routine laboratory tests which were done at each visit were the following: leucocyte count, hemoglobin

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estimation, throat culture, sedimentation rate, and Weltmann serum coagulation reaction. Electrocardiograms, stethograms, and other procedures were carried out as indicated.

The serum coagulation test, devised by Weltmann in 1930,[1] was an outgrowth of the observation that the coagulation temperature of human blood serum varies in different diseases, and that this coagulability is affected by the addition of electrolytes before heating. Less electrolyte was required in the presence of cirrhosis of the liver and chronic proliferative diseases than in the presence of acute infections such as lobar pneumonia. By varying the amounts of electrolyte added to the blood serum before heating, Weltmann developed the test which now bears his name.

METHOD

One-tenth cubic centimeter of unhemolyzed blood serum is added to each of ten test tubes containing 5 c.c. of varying concentrations of $CaCl_2$ arranged as shown in Table I.

TABLE I

TUBE NO.	1	2	3	4	5	6	7	8	9	10
CONC. OF $CaCl_2$ PER CENT	0.10	0.09	0.08	0.07	0.06	0.05	0.04	0.03	0.02	0.01

These tubes are then heated in boiling water for fifteen minutes, after which the test is read. The number of tubes in which evident flocculation occurs, rather than mere turbidity, is known as the coagulation band (C.B.). Coagulation occurs more readily in the tubes containing higher concentrations of electrolyte, normally in the first six or seven tubes (C.B. = 6, C.B. = 7). Coagulation in less than six tubes is known as a shift to the left, or a shortening of the coagulation band. Coagulation in more than seven tubes is known as a shift to the right, or a lengthening of the coagulation band.

A coagulation band of 6 or 7 has been found to be remarkably constant for normal sera. In exudative conditions, such as lobar pneumonia, there is a shift to the left, and in proliferative conditions, such as chronic fibrotic tuberculosis, there is a shift to the right. In marked congestive heart failure and in cirrhosis of the liver there is a shift to the right. There are characteristic changes in other conditions, such as parenchymatous liver disease.[2] The test has been used in the study of malignant disease,[3] typhoid fever,[4] syphilis,[5] disease of the kidneys,[6] and other conditions.[7-11]

RESULTS

A. *The Weltmann Reaction in Varying Clinical Conditions.*—Short coagulation bands of 5 or less were noted in acute rheumatic fever, with aching of joints with or without swelling or fever, and in some patients with exacerbations of chronic arthritic pains. Some patients had arthritic pains, in the absence of acute rheumatic fever, with a normal coagulation band on one such occasion and a shortened coagulation band on another, while the clinical condition remained apparently the same. The one patient with chorea continued to have a normal coagulation band throughout her illness.

In one patient (History No. 191202), a boy, 8 years of age, a coagulation band of 5 and a corrected sedimentation rate of 6 mm. per hour

were noted after the boy had had epistaxis twice during the preceding week, but appeared otherwise normal. A week later the child was admitted to the hospital with acute rheumatic polyarthritis, and at that time had a sedimentation rate of 32 mm. per hour and a coagulation band of zero. After convalescence the Weltmann reaction returned to a normal range of 6 or 7, and has remained so for over a year. The coagulation band was normal for two weeks before the sedimentation rate reached normal limits. This earlier return of the coagulation band to normal has been noted in other cases of rheumatic fever.[9]

A Weltmann reaction with a coagulation band of 5 was observed in two patients whose throat cultures yielded 25 per cent beta hemolytic streptococci at that time or several weeks earlier. There were one hundred twenty instances of mild colds or coughs without fever, and in four of these a coagulation band of 5 was noted, as compared with an elevated sedimentation rate in forty-six. When there were associated fever and cough, however, seven short coagulation bands were obtained.

In four instances a short coagulation band was found in a pregnant patient, but these same patients had normal coagulation bands at either earlier or later dates during the same pregnancies.

There were two patients with persistently elevated sedimentation rates. The first (History No. 107988) had pelvic thrombophlebitis in 1939. Her sedimentation rate had been elevated long before this, and she suffered with rheumatoid arthritis. She complained of occasional mild discomfort, and had sedimentation rates between 23 and 49 mm. per hour, corrected, during a thirteen-month period of observation in 1940 and 1941. During this time her coagulation band was always 6 or 7, and she was well except for an occasional cold. The second patient (History No. 150784) with a persistently elevated sedimentation rate (12 to 24 mm. per hour, corrected) had a swollen ankle or slightly aching knee at times, and suffered with mild chronic arthritis. However, her coagulation band was reduced (C.B. = 5) only on one occasion, when she had a temperature of 99.4° orally, and swelling and tenderness of a finger joint which were relieved by aspirin.

There was no clinically quiescent patient with a persistently abnormal Weltmann reaction, nor was there a patient with acute rheumatic fever and normal Weltmann reactions at that time. We could discover no relationship between persistently prolonged coagulation bands and the progressive development of rheumatic heart disease in the patients observed during the period of this study.

B. *Clinical Significance of Abnormal Coagulation Bands and Elevated Sedimentation Rates.*—The results obtained with the Weltmann serum coagulation test and the erythrocyte sedimentation rate will be considered first as to the significance of a normal result, and then as to the significance of an abnormal result.

There were 570 Weltmann tests on the eighty patients with rheumatic heart disease (Table II). Among the 449 Weltmann tests which fell within the normal limits, only twenty-seven, or 6.01 per cent, were obtained when the patients had symptoms or signs of rheumatic activity or other evident disease. Similarly, of the 318 normal sedimentation rates, twenty-two, or 6.97 per cent, were obtained in the presence of clinically evident disease activity which could be expected to be reflected in elevated rates.

TABLE II

ASSOCIATION OF COAGULATION BANDS AND SEDIMENTATION RATES WITH SYMPTOMS

	NO SYMPTOMS	SYMPTOMS	TOTALS
SHORT COAGULATION BAND			
Normal Sedimentation Rate	10	4	
Elevated Sedimentation Rate	9	19	
Totals	19	23	42
NORMAL COAGULATION BAND			
Normal Sedimentation Rate	246	13	
Elevated Sedimentation Rate	176	14	
Totals	422	27	449
PROLONGED COAGULATION BAND			
Normal Sedimentation Rate	40	5	
Elevated Sedimentation Rate	25	9	
Totals	65	14	79
TOTAL			570

Thus, in a single determination a *normal* coagulation band and a *normal* sedimentation rate were equally accurate (93.9 and 93.1 per cent, respectively) in indicating the absence of clinical activity of disease. When the results of these tests were *abnormal,* however, the correlation between the condition of the patient and the Weltmann reaction or sedimentation rate was not so evident.

There were, in all, 252 tests in which the sedimentation rate was elevated. Of these, forty-two, or 16.6 per cent, occurred in association with active disease; the rest were noted after periods of quiescence of the rheumatic process, which has been interpreted as presumably indicating that the disease was still active pathologically. Of seventy-nine Weltmann tests with a shift to the right, there was an incidence of 17.7 per cent in which there were symptoms. The remainder of tests with a prolonged coagulation band were found in cases of clinically inactive disease, and may reflect proliferative healing processes, perhaps eventually resulting in valvular scarring. In contrast, 54.7 per cent of the forty-two Weltmann tests with a shift to the left were associated with clinically evident disease activity.

It is seen that a shift to the left of the coagulation band may mean a clinically active disease process, and a shift to the right a proliferative healing process without evident clinical activity.

On twenty-eight occasions both an elevated sedimentation rate and a shortened coagulation band were present. In nineteen of these tests, or 67.8 per cent, there was evidence of clinical activity.

Five hundred six tests of each type were made when symptoms or signs of active disease were not noted. On such occasions there were 210 elevated sedimentation rates and 84 abnormal coagulation bands. Prolonged coagulation bands were more common than shortened coagulation bands when no symptoms were present. This again suggests that a shift to the right may reflect proliferative healing processes in the absence of clinical activity.

C. *Statistical Relationship Between Weltmann Reaction and Sedimentation Rate.*—In 610 instances the same specimens of blood were used for a determination of the coagulation band and of the erythrocyte sedimentation rate (Wintrobe method, with correction for volume of packed red cells). The distribution of these results is shown in Table III. Dr. Marie Cakrtova, of the Statistical Department of the Johns Hopkins Hospital, was kind enough to subject these figures to statistical analysis, and her preparation and analysis of Tables IV and V form the basis for this part of the discussion.

TABLE III

COMPARISON OF COAGULATION BAND AND CORRECTED ERYTHROCYTE SEDIMENTATION RATE

	COAGULATION BAND											
	0	1	2	3	4	5	6	7	8	9	10	
CORRECTED SEDIMENTATION RATE (MM./HR.)												TOTALS
0 – 10	0	0	0	0	1	13	115	164	38	7	0	338
11 – 20	0	0	0	0	1	15	70	53	23	0	0	162
21 – 30	0	0	0	1	2	8	34	33	9	1	0	88
31 – 40	1	0	1	1	1	1	4	5	4	1	0	19
41 – 50	0	0	0	0	1	0	0	1	0	0	0	2
51 – 60	0	0	0	0	0	0	0	1	0	0	0	1
TOTALS	1	0	1	2	6	37	223	257	74	9	0	610

TABLE IV

COMPARISON OF COAGULATION BAND AND CORRECTED ERYTHROCYTE SEDIMENTATION RATE

COLUMN NO.	I	II	III	IV	V	VI	VII	VIII	IX	X
	0-5 (SHORTENED C.B.)			6-7 (NORMAL C.B.)			8-10 (PROLONGED C.B.)			
SEDIMENTATION RATE = MM./HR.	NO. TESTS	%	RATE %	NO. TESTS	%	RATE %	NO. TESTS	%	RATE %	TOTAL
0 – 10	14	29.79	4.14	279	58.12	82.54	45	54.22	13.31	338
11 – 20	16	34.04	9.88	123	25.62	75.93	23	27.71	14.20	162
21 and over	17	36.17	15.45	78	16.25	70.91	15	18.07	13.64	110
TOTAL	47	100.00		480	100.00		83	100.00		610

% = Percentage of total number of tests with this coagulation band.
Rate % = Percentage of total number of tests with this sedimentation rate.
C.B. = Coagulation band.

The results of the Weltmann serum coagulation test can be conveniently divided into three groups: one with a coagulation band of 0 to 5, inclusive (i.e., a shortened C.B.); one with a coagulation band of 6 or 7 (i.e., a normal C.B.); and one with a coagulation band of 8 to 10 (i.e.,

a prolonged C.B.). The results grouped in this manner are shown in Table IV. The percentage distribution of the sedimentation rates is similar in the normal group (Column V) and in the group with the prolonged coagulation bands (Column VIII). Both of these groups, however, differ from the group with a shortened coagulation band (Column II). The increasing rate percentage in the group with a shortened coagulation band (Column III) suggests that the shorter the coagulation band, the greater the probability of a higher sedimentation rate.

TABLE V

COMPARISON OF OBSERVED AND THEORETICAL DISTRIBUTIONS OF COAGULATION BANDS IN SEDIMENTATION RATE GROUPS

COLUMN NO.	I	II	III	IV	V	VI
	0-5 (SHORTENED C.B.)		6-7 (NORMAL C.B.)		8-10 (PROLONGED C.B.)	
SEDIMENTATION RATE: MM./HR.	OBSERVED	THEORETICAL	OBSERVED	PERCENTAGE DISTRIBUTION	OBSERVED	THEORETICAL
0 – 10	14	27.32	279	58.12	45	48.24
11 – 20	16	12.04	123	25.62	23	21.26
21 and over	17	7.64	78	16.25	15	13.49
TOTAL	47	47.00	480	100.00	83	82.99

This fact can be demonstrated more strikingly in another way. In Table V the percentage distribution of the normal group (Column IV) is used as the theoretical distribution, and from this as a standard is calculated the expected number of cases at the different sedimentation rates for the groups with shortened coagulation bands (Column II) and prolonged coagulation bands (Column IV), respectively. The expected number of tests at the different sedimentation rates for the groups with prolonged coagulation bands (Column VI) is not far from the observed number for this group (Column V). In the group with shortened coagulation bands, however, the observed distribution (Column I) is quite different from the theoretical distribution (Column II). This difference in the group with a coagulation band of 0 to 5, inclusive, is statistically significant. There is a probability of less than one in one hundred of obtaining such a result by chance alone.

The group with sedimentation rates of 0 to 10, inclusive, is significantly different from the group with rates of 11 to 20, inclusive, and from the combined groups with rates of 11 and over. The last group contributes the most to the statistical significance of the differences between the observed and the expected number of tests.

Thus, there seems to be definite evidence that coagulation bands of 0 to 5, inclusive, are more frequently associated with higher sedimentation rates than are coagulation bands of 6 to 10, inclusive. The usefulness of this conclusion is limited by the fact that for statistical reasons the sedimentation rates over 20 had to be grouped together, leaving a

limited range of sedimentation rates. More extensive experience may demonstrate the relationship between lower coagulation bands and higher sedimentation rates on a more gradual scale.

DISCUSSION AND CONCLUSIONS

To ascertain the value of the Weltmann serum coagulation test in detecting occult rheumatic activity, two things must be done. First, the variation in the coagulation band with easily recognized signs of disease activity should be determined, measuring the ability of the test to confirm known signs of rheumatic activity; for, if the Weltmann test does not confirm obvious manifestations, its value in indicating occult processes is open to debate. After the sensitivity of this reaction to recognized clinical activity is thus ascertained, the next problem is to evaluate its usefulness in indicating occult rheumatic activity.

The results in this series seem to show that a *normal* sedimentation rate and a *normal* coagulation band are equally significant in indicating the absence of clinical disease activity, as demonstrated by their infrequent association with signs or symptoms of an active disease process. An *abnormal* Weltmann reaction, especially a short coagulation band, was more frequently associated with clinical disease activity than was an elevated sedimentation rate. The larger proportion of elevated sedimentation rates in the absence of clinical activity would suggest that an *abnormal* Weltmann result would be a more reliable indicator of the presence of an active process, and that this test would be of value in detecting possible subclinical inflammatory activity, such as may exist in patients with progressive rheumatic heart disease.

The second aspect of the problem defined earlier would involve prolonged observation of a group of patients, to see whether patients with abnormal coagulation bands developed rheumatic heart disease more frequently than those with normal coagulation bands, in the absence of easily recognized signs of rheumatic activity. Only in this way could one draw valid conclusions as to the value of this test in detecting occult or subclinical rheumatic activity. This report covers only the first phase of the problem as described above, and certain other of our results.

While the period of study of these cases has been insufficient to draw any conclusion as to the relationship between a persistently lengthened coagulation band, a normal coagulation band, or a shortened coagulation band and the rate of progression of the rheumatic process, the results thus far obtained suggest that this test may be of value in pursuing such a study. It is suggested that the Weltmann serum coagulation test be used, not to supplant the erythrocyte sedimentation rate in the study of rheumatic fever and the development of rheumatic heart disease, but as an added procedure, based upon certain changes in the blood proteins, which may shed light upon the still unknown underlying process.

The infrequent occurrence of a shortened coagulation band in association with colds and coughs in the absence of fever, and the presence of a Weltmann reaction with a shift to the left when fever is added to these symptoms, suggest that inflammation and changes in the blood proteins are present under the latter circumstances, and indicate another application of the Weltmann test.

The significant correlation between shortening of the coagulation band and elevation of the erythrocyte sedimentation rate, pointed out in part C of the RESULTS, fits in with several other interesting observations. Shedlovsky and Scudder[12] made a comparison of erythrocyte sedimentation rates and electrophoretic patterns of normal and pathologic human blood, and noted that "an increase of alpha globulin seems to take place, as well as an increase in sedimentation rates, when there is present any considerable inflammation or tissue destruction, irrespective of its cause." They presented a graphic correlation between sedimentation rates and alpha globulin levels. Scherlis and Levy,[13] investigating the mechanism of the Weltmann serum coagulation test, showed that the length of the coagulation band depends upon qualitative rather than quantitative changes in the blood serum. They subjected the same specimen of blood to an electrophoretic analysis and a Weltmann test in thirty-three instances, and demonstrated an inverse relationship between the percentage of alpha globulin in the blood and the length of the coagulation band.

Thus, while one group noted that an elevated sedimentation rate seems to be associated with an increase of alpha globulin, another group demonstrated that a shortening of the coagulation band is associated with an increase of alpha globulin. The present paper independently points out the statistically significant correlation between elevated sedimentation rates and shortened coagulation bands. It would seem very likely, therefore, that a somewhat similar, although not identical, mechanism underlies both tests.

The lack of correlation between prolongation of the coagulation band and elevation of the sedimentation rate may be explained by the fact that a lengthening of the coagulation band is related to a *decrease* in the percentage of alpha globulin and an accelerated sedimentation rate has been shown to be related to an *increase* in alpha globulin. Perhaps both tests are largely dependent upon variations in the alpha globulin of the blood, but the Weltmann reaction is more sensitive over the range where alpha globulin percentages are lowest.

SUMMARY

1. The variation of the Weltmann reaction with different clinical conditions in patients with actual or potential rheumatic heart disease has been described.

2. There was no patient with clinically quiescent disease with a persistently abnormal Weltmann reaction, nor was there a patient with acute rheumatic fever and normal Weltmann reactions at that time.

3. There was no relationship between persistently prolonged coagulation bands and the progressive development of rheumatic heart disease in the patients observed during the course of this study.

4. In a single determination, a normal coagulation band and a normal sedimentation rate were equally accurate (93.9 and 93.1 per cent of 449 tests, respectively) in indicating the absence of clinical disease activity.

5. An abnormal Weltmann reaction, especially a shortened coagulation band, was more frequently associated with clinical disease activity than was an elevated sedimentation rate.

6. The statistically significant correlation between elevated sedimentation rates and shortened coagulation bands was pointed out, and the relationship of these results to an increase in alpha globulin in the blood was discussed.

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ROENTGENOLOGIC AND ELECTROCARDIOGRAPHIC CHANGES IN THE NORMAL HEART DURING PREGNANCY

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MANY women who are examined for the first time late in pregnancy present clinical evidence of questionable cardiac enlargement, symptoms and signs suggestive of myocardial insufficiency, such as dyspnea, edema of the ankles, and possibly occasional râles at the base of the lungs, and, in roughly 10 per cent, an apical systolic murmur and an accentuated pulmonic second sound. It is important for the obstetrician to know whether organic heart disease exists, for the management of protracted labor or possible dystocia will most certainly be influenced by such a diagnosis. Whether or not the heart is able to support the load of pregnancy and carry the patient successfully through labor is often difficult to ascertain clinically, and various laboratory procedures have been suggested to determine the severity of the cardiac state. The methods most frequently employed are the roentgenogram and the electrocardiogram. All patients referred for consultation to the Cardiac-Obstetrical Clinic from the Prenatal Clinics have roentgenograms in the three standard positions, posteroanterior, left oblique, and right oblique, with esophagram, before being examined in the Cardiac Clinic. During the past five years, we have been impressed by the frequency of roentgenologic reports of "enlargement of the left auricle in the right oblique view and straightening of the left upper border of the heart on the posteroanterior view, compatible with the diagnosis of mitral valvular disease" on patients who presented no definite history, symptoms, or signs of organic heart disease. A search of the literature failed to reveal any observations on encroachment on, or backward displacement of, the esophagus associated with pregnancy, and there was considerable divergence of opinion as regards the cause of such changes as have been reported in the roentgenogram and electrocardiogram. Most investigators agree that the heart shadow increases in size during pregnancy, but whether this is as a result of essential cardiac hypertrophy, with or without dilatation, as suggested by Jensen and Norgaard[1] and their chief, Gammeltoft,[2] or whether it is produced primarily by rotation and displacement of the heart, as suggested by most American workers, particularly Hamilton[3] and his co-workers, is still undecided.

In 1922, Smith[4] observed the presence of left axis deviation in the electrocardiogram of a woman who was eight months pregnant. He followed her throughout her labor and noted that, with descent of the fetus, this became less marked. Thirty minutes post partum it had

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completely disappeared. McIlroy and Rendel,[5] Konki,[6] Jensen and Norgaard,[1] and Carr, Hamilton, and Palmer[7] have recorded similar observations. Pardee[8] was the first to describe a deep Q wave in Lead III of the electrocardiogram, and Konki[6] and Carr and Palmer[9] noted inversion of the T wave in Lead III during the later months of pregnancy. These observations have been variously interpreted, but, in general, two schools of thought exist: that these changes are a result of cardiac hypertrophy and dilatation, or that they indicate displacement and rotation of the heart.

The literature on roentgenologic changes in the heart during pregnancy is even more confused. Gerhardt[10] observed that during the later months of pregnancy the heart assumed a mitral shape. Hyneman[11] stressed the elevation of the diaphragm and the transverse position of the heart during the third trimester. This was discounted by Jensen and Norgaard, who found an increase in the diameters of the heart in, roughly, one-third of their cases. Hamilton and Thomson[3] emphasized not only the general enlargement of the heart, but also the increase in the so-called normal hilar markings which may be mistaken for abnormal pulmonary congestion by one unfamiliar with the roentgenograms of pregnant women. Landt and Benjamin[12] called attention to the encroachment on the anterior clear space by the right ventricle in the lateral view.

In view of the vast differences of opinion, and the fact that no definite conclusions may be drawn from the work quoted, it was thought that a resurvey of the problem, using slightly different techniques, was warranted.

For purposes of study, patients who were in the first trimester of their pregnancy, and had no history, signs, or symptoms of heart disease were referred to us from the prenatal clinics. They were then examined by us to confirm the opinion that they were perfectly normal. Serial roentgenograms in the three standard positions were taken and repeated at three-month intervals during their gestation, and one and two or more months post partum. Electrocardiograms, using the two-string electrocardiograph and thus securing Leads I and III simultaneously, in order to calculate accurately the electrical axis, were also taken, and these were repeated at four-week intervals. All patients who did not continue under our observation for their entire pregnancy and post-partum period were excluded from the study group. A large number of cases were observed, but only eighteen were followed throughout the desired period, and this is the group reported. All the observations on the others confirmed those in this group.

Electrocardiographic Changes.—The most outstanding changes in the electrocardiogram were confined to Lead III. A prominent and, at times, deep Q wave and inversion of the T wave were present in five cases, and the T wave became negative and then positive post partum without alteration of the Q wave in four cases. No abnormalities of QRS or the RS-T segments appeared. Although there was no absolute

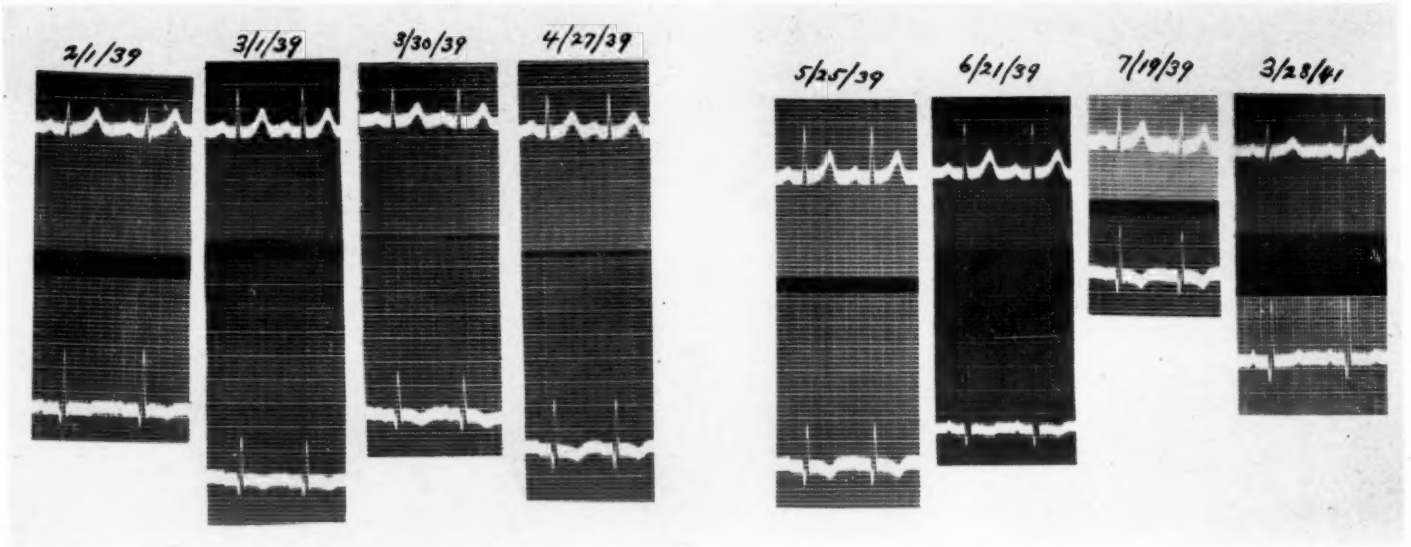

Fig. 1.—Electrocardiograms of Patient A. G., Case No. 9. Patient delivered of normal full-term baby on Aug. 31, 1939. Note the inversion of the T wave in Lead III; it returned to normal post partum. The Q wave was constant throughout in this lead.

or invariable rate of electrical axis deviation, nevertheless the trend for the group confirmed the observations of Carr and Palmer[9] that the axis undergoes a shift toward the left during the first and second trimesters of pregnancy, and then swings to the right. This change in the angle of the axis was not pronounced on superficial inspection of the electrocardiograms, but when measurements were made, and the angle of axis direction was plotted according to Carter, Richter and Greene's[13] modification of the Einthoven method, the shift was obvious. In a few instances the difference of the angle varied as much as 28 degrees, but in most instances the magnitude of the shift was, roughly, 15 degrees (Table I, Figs. 1 and 2).

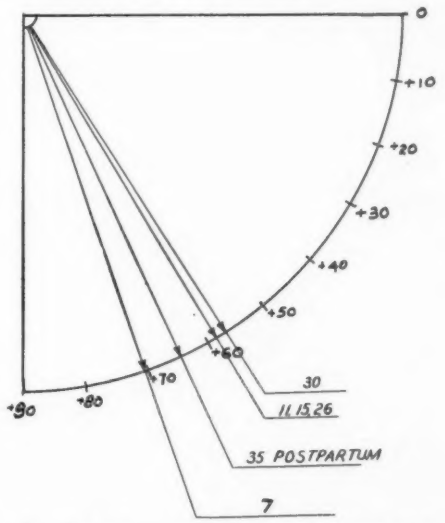

Fig. 2.—Patient M. S., Case 18. Illustration of the shift of the angle of the electrical axis in a rather characteristic fashion. The numbers on the arrows indicate the time of gestation in weeks.

TABLE I

ELECTROCARDIOGRAPHIC OBSERVATIONS

CASE NUMBER	PATIENT	MINIMUM ANGLE (DEGREES)	MONTH	MAXIMUM ANGLE (DEGREES)	MONTH	$Q_3 - T_3$ CHANGES
1	I. H.	77	4	59	8	
2	K. R.	27	3	9	4	Deep Q, negative T
3	C. M.	43	3	22	6	
4	A. F.	73	3	43	7	
5	S. K.	–11	4	–16	7	
6	F. O'H.	31	3	10	7	
7	T. R.	24	3	–15	4½	Negative T
8	V. B.	9	3	–½	4	
9	A. G.	71	3	56	4	Negative T
10	E. P.	45	3	17	8	Deep Q, negative T
11	M. G.	35	3	26	6	
12	D. P.	75	3	54	5	Deep Q, negative T
13	M. H.	75	4½	62	7	Deep Q, negative T
14	E. C.	13	7	–14	6	
15	R. G.	9	3	–½	6	Negative T
16	B. P.	14	3	11	7	
17	B. DiG.	45	3	36	9	Negative T
18	M. S.	71	2	51	7	Deep Q, negative T

Fig. 3.—Roentgenograms of Patient A. G., Case 9. Patient ten weeks pregnant.

Fig. 4.—Roentgenograms of Patient A. G., Case 9. Patient twenty-six weeks pregnant. Note the invasion, and moderate displacement backwards, of the esophagus in right anterior oblique view.

Fig. 5.—Roentgenograms of Patient A. G., Case 9. Patient thirty-four weeks pregnant. Note the marked change in the esophagus as compared to Fig. 4.

Fig. 6.—Roentgenograms of Patient A. G., Case 9. Post partum. The length of time which elapsed between delivery date and these roentgenograms was due to difficulty in getting the patient to return.

TABLE II

ROENTGENOLOGICAL OBSERVATIONS

CASE NUMBER	PATIENT	STRAIGHTENING OF LEFT BORDER	PROMINENCE OF PULMONARY CONUS	INVASION OF ANTERIOR WALL OF ESOPHAGUS	MARKED ENCROACHMENT ON ESOPHAGUS	ELEVATION OF LEFT MAIN BRONCHUS
1	I. H.			Y		
2	K. R.				Y	
3	C. M.			Y		
4	A. F.	Y		Y		
5	S. K.			Y		
6	F. O'H.			Y		
7	T. R.		Y			
8	V. B.					
9	A. G.				Y	
10	E. P.					
11	M. G.			Y		
12	D. P.	Y	Y			
13	M. H.		Y			
14	E. C.			Y		
15	R. G.			Y		
16	B. P.					
17	B. DiG.					Y
18	M. S.					

Y represents the occurrence of a change.

Roentgenologic Changes.—Several distinct changes were noted in the roentgenograms, and these have been tabulated (Table II). The most frequent abnormality was an encroachment on the anterior surface of the esophagus in the region of the left auricle. In the majority of instances the esophagus as a whole was not displaced, but a definite indentation of the anterior wall was seen (Figs. 3, 4, 5, and 6). There were ten such instances, but in two subjects there was marked invasion, with moderate backward displacement of the barium-filled esophagus. There were two instances of straightening of the left upper border of the cardiac silhouette, and three instances of prominence of the pulmonary conus.

DISCUSSION

Previous roentgenologic studies of the heart in pregnancy have been limited primarily to posteroanterior views. Landt and Benjamin[12] mention encroachment on the anterior clear space by the right ventricle. Studies in the oblique positions have been found to be particularly valuable in demonstrating cardiac enlargement in persons with short, broad chests. It therefore seemed probable that the right oblique position, with an esophagram, might be similarly useful in studies of pregnant women. Clauser[14] found a suggestion of generalized enlargement of the heart, with an increasing tendency toward a transverse position and kinking of the great vessels. Jensen[1] studied 157 women roentgenologically from the onset of pregnancy until the end of the puerperium, using the posteroanterior view. He found that 33 per cent of these women had a demonstrable increase in the cardiac diam-

eters. This occurred before the elevation of the diaphragm took place. This change was not constant, and was more likely to be present in those women who were suffering from what he terms "gestatory heart disease." In his electrocardiographic studies, he attributed the reduction in the amplitude of the R wave and the increase in the depth of the S wave in Lead III, with a resultant shift in the electrical axis, and the early occurrence of this change, to hypertrophy and dilatation. Most investigators disagree with this. Although it has been shown[15, 16] that the cardiac output is increased from one-third to one-half during the latter part of pregnancy, it is also true that moderately increased cardiac work does not necessarily lead to hypertrophy of the normal heart. Furthermore, it has been demonstrated that no observable cardiac hypertrophy is found in the guinea pig, cat, or dog, during pregnancy.[17] The appearance of a Q wave and the negativity of the T wave in Lead III are easily explained as a result of a positional shift of the heart. Cohn and Raisbeck,[18] by rotating leads taken directly from the chest in a clockwise manner through an arc from 80 to 120 degrees, produced curves showing typical, large Q waves in Lead III. Inversion of the T waves in this lead similarly indicates a change in the position of the heart. The inconstancy of these changes weakens the argument for hypertrophy, for this should be present in all or a majority of pregnant women. In the cases studied, although rather marked changes occasionally occurred, the patients never manifested any evidence of heart disease. A further point against hypertrophy is that often these changes disappear toward the end of pregnancy, when there is no reason to believe that hypertrophy should cease. It seems more logical to attribute the observed changes to displacement upwards and laterally, with rotation around the long axis of the heart. The relation of the long and transverse diameters of the chest to the transverse diameter of the heart during pregnancy will influence the degree of shift which occurs. Thomson, Cohen, and Hamilton,[19] in comparing the relationship of the electrocardiographic changes in the different types of chest, found that the Q- and T-wave alterations were more evident when the height of the diaphragm most markedly affected the position of the heart.

In reviewing our roentgenograms we were impressed by the similarity of the changes associated with pregnancy and those encountered in mitral disease. The posteroanterior view of the heart in mitral stenosis almost invariably presents a characteristic appearance. Its chief distinguishing features are straightening or bulging of the left upper border as a result of prominence of the pulmonary conus and the left auricle. Other abnormalities include elevation of the left main bronchus by the enlarged left auricle, the engorged pulmonary veins, or both, increased hilar shadows due to the dilated pulmonary artery branches, and clouding of the lung fields caused by pulmonary congestion. The

fact that the left upper border of the cardiac silhouette may become straightened during pregnancy in normal women is so well known that Gerhardt's phrase "mitral shape without mitral lesion" has been used to describe the picture.[10] Lately, particular attention has been directed to the use of roentgenologic methods in the differentiation of enlargement of the individual chambers of the heart, and, in this connection, study of the barium-filled esophagus in the right oblique position is considered of paramount importance in the diagnosis of the enlargement of the left auricle which is so commonly associated with mitral disease. Evans[20] states that "the alteration of the form of the impression (i.e., left auricle) in the right oblique view in mitral stenosis is acknowledged as a valuable sign. Moderate distension of the left auricle produces a conspicuous left auricle impression in the right oblique position, but the significance of slight prominence of the impression is often difficult to assess. When adjudicating whether the curve is normal or abnormal in the adult, it is necessary to pay particular attention to the upper segment of the impression because abruptness of this portion of the curve is caused by the atrial prominence of the left auricle. This is fed by the pulmonary veins which become distended in mitral stenosis. Thus, the barium meal is slightly delayed at the commencement of the impression and produces a sharp angulation to the right as viewed in this position." Recent investigations have shown that backward displacement of the esophagus in this position is not invariably caused by left auricular enlargement,[21] but may be the result, in a small percentage of cases, of a variety of conditions, e.g., congenital heart disease, aortic insufficiency, hypertension, auricular fibrillation, complete heart block, and aneurysm of the heart. It may also be present during gestation in normal women. In two of the eighteen women in the present series this phenomenon was conspicuous, and in eight of the others it was present in a lesser degree.

It seems possible to account for the indentation of the esophagus by some generalized increase in the size of the heart during pregnancy. The work of Thomson, Hirsheimer, Gibson, and Evans[22] has shown that the total blood volume increases from early pregnancy to the ninth lunar month; during the tenth month there is a definite diminution, and by the second month of the puerperium it has been restored to the normal level. The time at which the reduction takes place is usually the thirty-fourth to the thirty-sixth week. Burwell and his co-workers[23] demonstrated that the cardiac output shows a similar trend of comparable magnitude. In our roentgenograms which were taken at the thirty-fourth week, the esophageal indentation that had been present earlier in pregnancy had practically disappeared. This suggests that the increase in blood volume causes cardiac enlargement by increasing the quantity of blood in the heart. Our studies lend no support to the view that cardiac hypertrophy occurs during normal pregnancy. If the enlargement were due to hypertrophy, one would

expect, if it could occur at all, a gradual decrease in size, rather than the relatively sudden change which takes place at a particular time in the pregnancy.

CONCLUSIONS

1. Eighteen pregnant women were followed from the early months of pregnancy to the post-partum period by serial roentgenographic studies in the posteroanterior and left and right oblique views, with esophagrams, and, also, by monthly electrocardiograms, using a two-string galvanometer to measure the changes in the electrical axis accurately.

2. The outstanding roentgenologic change was an indentation of the anterior wall of the esophagus. This is attributed to an increase in the size of the heart as a result of the increased amount of blood it contains, in consequence of the increased blood volume. The transverse diameter of the heart was increased during pregnancy, but, as the diaphragm becomes elevated, it is difficult to assess the relative value to be placed on shift of position and increase in blood volume.

3. The principal electrocardiographic changes were the frequent development of a deep Q wave and negative T wave in Lead III. The electrical axis changed, on the average, about 15 degrees. The reason for so slight a change when, roentgenographically, the position of the heart would suggest a much greater shift in the axis may be attributed to the fact that the heart is not only shifted transversely, but is also rotated in its long axis.

We wish to express our appreciation for the assistance rendered by Miss Eveline D. Reynolds, who took the electrocardiograms, and to Dr. Richard A. Rendich, Director of the X-Ray Department of the Kings County Hospital.

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THE EFFECT OF TRICHLORETHYLENE ON THE HUMAN, CANINE, AND RABBIT ELECTROCARDIOGRAM

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ALTHOUGH trichlorethylene has been used in the treatment of angina pectoris,[1, 2] its action on the cardiovascular system has not been extensively investigated. Only two short reports dealing with its cardiovascular effects are available,[3, 4] and both came from the same group of workers. Since trichlorethylene may be useful in the prevention and treatment of angina pectoris, an extensive study of its action was undertaken. In this paper the electrocardiographic changes produced by the administration of trichlorethylene to human, canine, and rabbit subjects are reported.

EXPERIMENTS

Rabbit Studies.—In these experiments control electrocardiograms were taken after the animals had been resting in a basal-like state[5] for fifteen minutes, and test records were taken during and after the inhalation of trichlorethylene. In the first three experiments, normal rabbits, not previously used for any kind of experimentation, were used, whereas, in the last two, the rabbits had been anesthetized with trichlorethylene every day for a week. All of the rabbits were practically of the same weight (5 to 6 pounds). In this way, the effects of trichlorethylene on the electrocardiograms of rabbits never before anesthetized and on rabbits subjected to repeated anesthetization were studied.

Fig. 1 presents a series of records obtained from a rabbit which had never before been anesthetized with trichlorethylene. *A* is the control record; *B* and *C* were made after 1 c.c. of trichlorethylene had been given by inhalation, *D*, *E*, and *F*, after another cubic centimeter had been given by inhalation, *G*, after trichlorethylene had been discontinued for about five minutes, and *H*, after trichlorethylene had been discontinued for about fifteen minutes. The following effects may be observed: marked slowing (*B* and *C*), pulsus bigeminus (*D*), and extrasystoles (*F*).

The records presented in Fig. 2 were obtained from the rabbit of Fig. 1 after the animal had been subjected to daily anesthetization for a week. *A* is the control record; *B*, *C*, *D*, *E*, *F*, and *G* were taken after 2 c.c. of trichlorethylene had been administered by inhalation, and *H*, after trichlorethylene had been discontinued for about fifteen minutes. The effects in this experiment include marked slowing (*B*, *C*, *D*, *E*, *F*, and *G*), inversion and obliteration of the P wave (*D* and *G*), and changes in the T wave—diphasic to inverted (*D*, *E*, and *F*).

Canine Studies—Four dogs, which weighed 35 to 40 pounds, were used in these experiments. They were anesthetized with nembutal, and electrocardiograms were made before and after trichlorethylene was given while the blood pressure, respiration, and kidney volume were being recorded on a kymograph. The effects of trichlorethylene on the blood pressure, respiration, and kidney volume of the dog will be dealt with in another paper. Trichlorethylene was administered in 1 c.c. amounts, approximately five minutes apart, first by inhalation, and then intravenously at about ten-minute intervals.

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In three of the dog experiments the effects of different concentrations of trichlorethylene were looked for. Giving too much of the drug was avoided because we wanted the animals to survive. In the other experiments (two), the effects of the quantity of the drug necessary to kill the animals were studied.

Fig. 3 includes a sequence of electrocardiograms from a dog that was used in the first series of experiments. *A* is the control record, *B* was taken after 6 c.c. of trichlorethylene had been administered by inhalation, *C*, after 1 c.c. of trichlorethylene had been given intravenously, *D*, after the second cubic centimeter had been given intravenously, *E*, after the third cubic centimeter had been given intravenously, and *F*, *G*, and *H*, after the fourth cubic centimeter had been given intravenously.

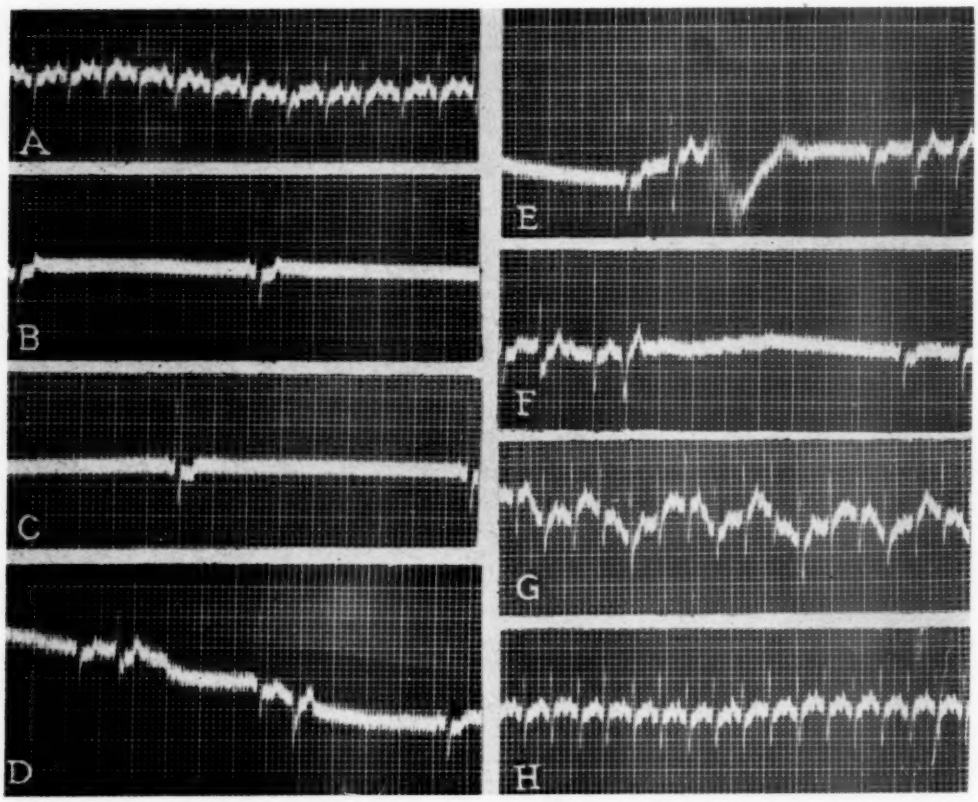

Fig. 1.

Study of these records reveals that significant electrocardiographic changes did not occur, even after 6 c.c. of trichlorethylene had been given by inhalation (*A* and *B*). Noteworthy electrocardiographic changes occurred in this experiment only after the drug had been given intravenously (*C* to *H*, inclusive). In *C* the rate is slower; in *D* the rate is slower still, and there are changes in the P wave; in *E* an ectopic beat occurs; in *F* and *G* the P wave is smaller; and in *H* the P wave is isoelectric.

The electrocardiograms presented in Fig. 4 were obtained from a dog in the second series of experiments. *A* is the control record, *B* was made after 5 c.c. of

trichlorethylene had been administered by inhalation, *C*, after 1 c.c. of trichlorethylene had been injected intravenously, *D*, after 3 c.c. of the drug had been injected intravenously, *E*, *F*, and *G*, after the sixth, seventh and eighth cubic centimeter of the drug had been injected, and *H*, as the dog died.

The electrocardiographic changes in this experiment were similar to those in Fig. 3, except for the changes associated with the death of the animal. Pulsus bigeminus (*C* and *D*) and complete block at the auriculoventricular node (*E*, *F*, and *G*) are the outstanding abnormalities in Fig. 4. The auriculoventricular block produced in this experiment was very likely associated with the large amount of trichlorethylene administered.

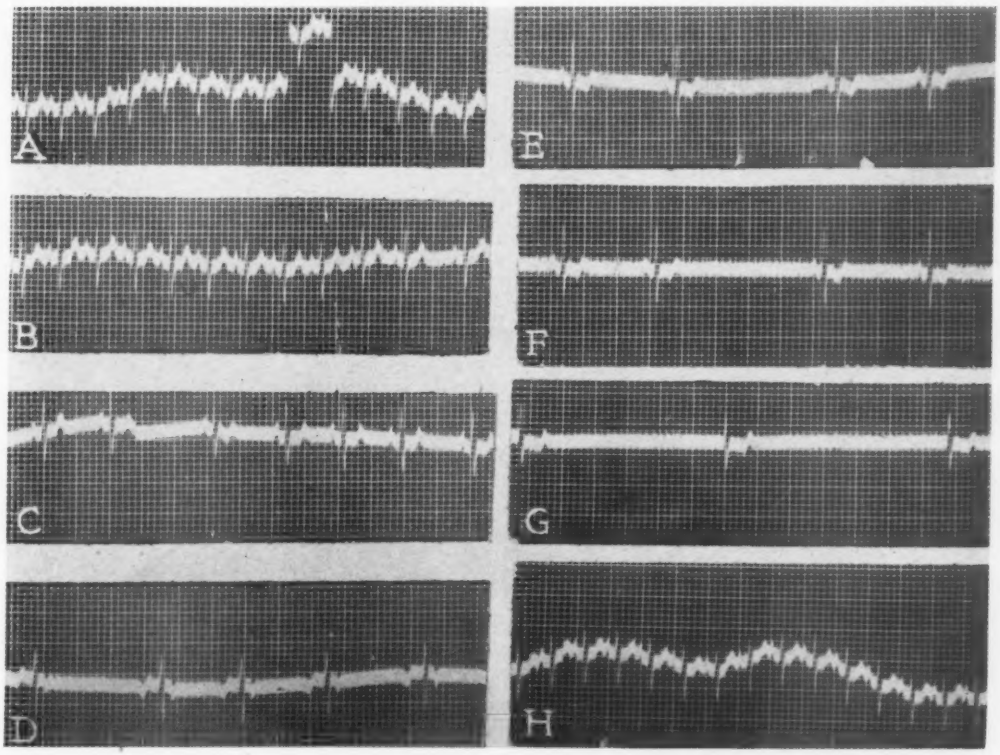

Fig. 2.

Human Studies.—The possible effects of a therapeutic dose of trichlorethylene (four to six deep inhalations from an ampoule broken in a kerchief) were watched for in these experiments. Six normal subjects and ten patients with cardiovascular disorders were employed. Electrocardiograms, sphygmograms, and blood pressure readings were taken before and after trichlorethylene was administered to the normal subjects. No sphygmograms were obtained from the subjects with cardiovascular disease.

The blood pressure readings presented in Table I were obtained from the normal subjects. Except in Subjects A and C, no significant changes in blood pressure took place after trichlorethylene was administered. Similarly, no significant changes

were observed in the electrocardiograms and sphygmograms from these subjects. The control and test sphygmogram and electrocardiogram from Subject B, reproduced in Fig. 5, illustrate these points.

The inhalation of trichlorethylene also did not produce any noteworthy changes in the blood pressure or electrocardiograms of the subjects with cardiovascular disease. Their blood pressure readings are given in Table II. Fig. 6 presents the electrocardiograms of Subject F.

TABLE I

BLOOD PRESSURE MEASUREMENTS ON NORMAL SUBJECTS

SUBJECT	SEX	AGE (YR.)	BLOOD PRESSURE* BEFORE	AFTER
A	M	34	110/62	92/70
B	M	40	135/95	130/95
C	F	28	134/90	120/84
D	M	28	120/84	120/70
E	M	37	126/90	120/90
F	F	27	124/86	124/76

*Before and after the inhalation of trichlorethylene.

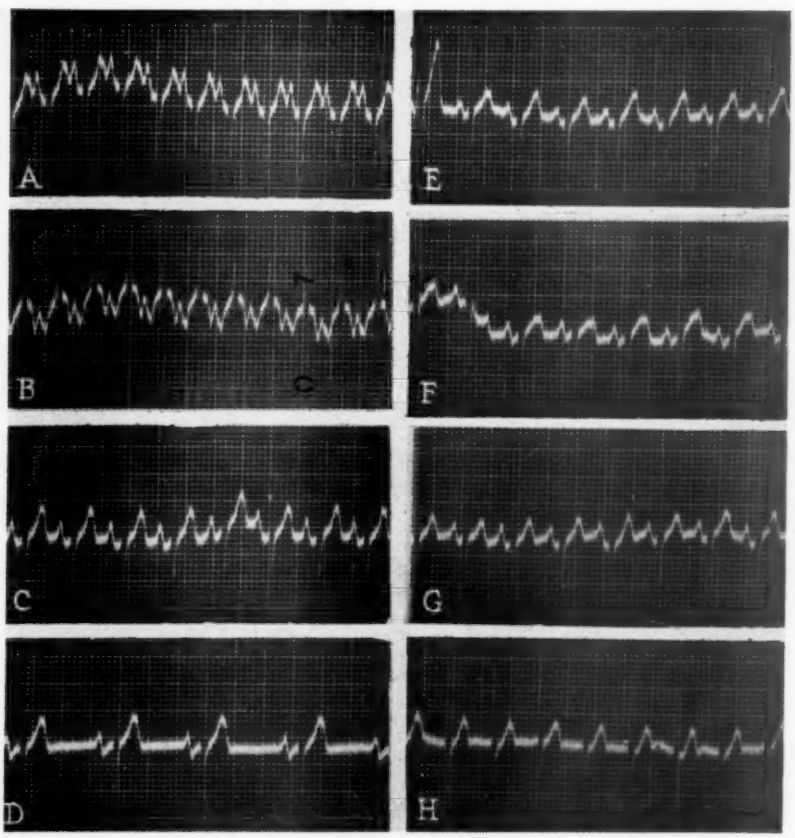

Fig. 3.

TABLE II

BLOOD PRESSURE MEASUREMENTS ON SUBJECTS WITH CARDIOVASCULAR DISEASE

SUBJECT	SEX	AGE (YR.)	DISEASE	BLOOD PRESSURE* BEFORE	AFTER
A	M	68	Arteriosclerosis	115/80	120/80
B	F	22	Paroxysmal tachycardia (amputation of left leg because of embolism)	135/100	140/110
C	F	68	Varicosities of lower extremities	150/100	150/100
D	F	56	Varicosities of lower extremities	120/80	110/70
E	M	56	Arteriosclerosis (Diabetes)	200/110	200/110
F	F	67	Arteriosclerosis	190/80	190/80
G	M	59	Thromboangiitis obliterans	135/85	140/80
H	M	64	Arteriosclerosis, angina pectoris, myocarditis	150/85	165/85
I	F	65	Arteriosclerosis	190/120	185/120
J	M	65	Varicosities of lower extremities	145/80	140/80

*Before and after the inhalation of trichlorethylene.

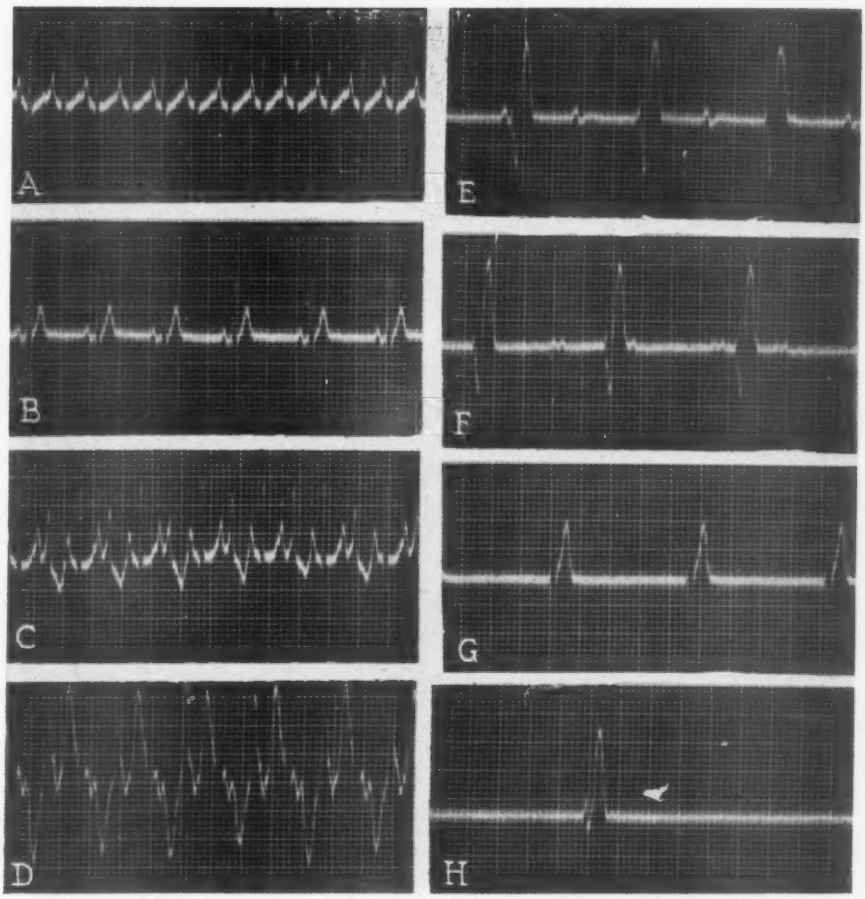

Fig. 4.

DISCUSSION

The electrocardiograms obtained from the rabbits which had never before been anesthetized with trichlorethylene and from those subjected to repeated anesthetization indicate that the drug affects the conducting mechanism and the muscle of the rabbit's heart. Evidence that there is an alteration in the conducting mechanism lies in the marked slowing and ectopic beats. Obliteration of the P wave and the changes in the T wave, on the other hand, are indications of its effect on the myocardium, especially since these changes were observed in the electrocardiograms obtained from the rabbits that were subjected to repeated anesthetization. Permanent electrocardiographic changes were not observed. Return to normal took place when the drug was withdrawn. Nevertheless, since P and T wave changes occurred after the rabbits had received trichlorethylene repeatedly, there is a possibility that permanent changes may take place.

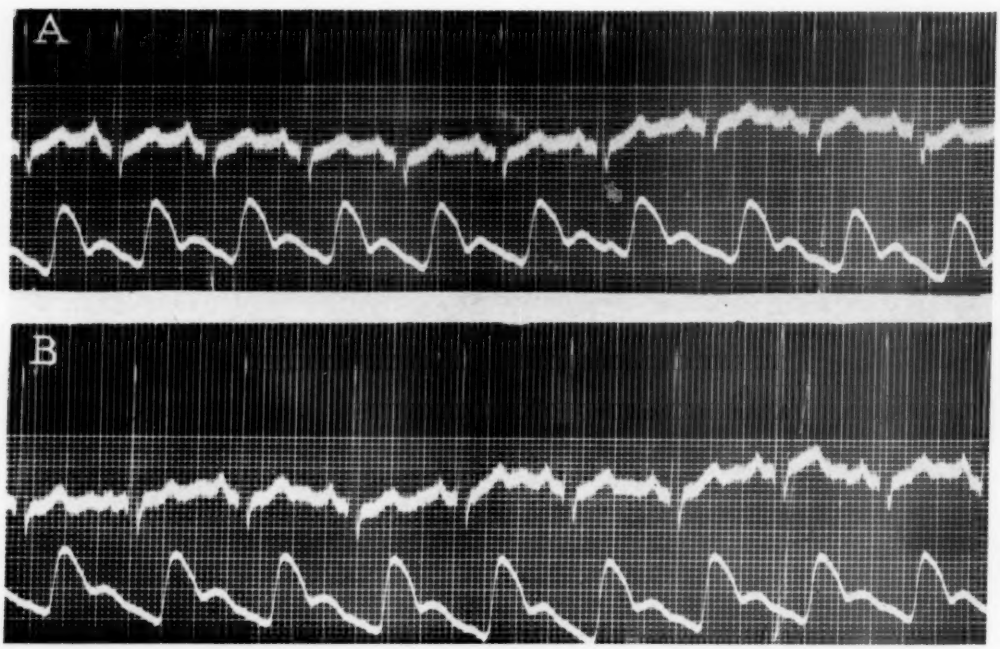

Fig. 5.

The dogs had never before received trichlorethylene, and consequently their electrocardiograms can be compared only with those obtained from the rabbits which had never before been anesthetized with the drug. If this is done, similarities are observed. The marked slowing and the presence of ectopic beats indicate an effect on the conducting mechanism of the dog's heart. The complete block shown in Fig. 4, as well as the

changes in the P wave, was probably caused by the comparatively larger amount of the drug employed in that experiment.

It is apparent that the administration of a therapeutic dose of trichlorethylene to normal human subjects or patients with cardiovascular disease does not produce significant electrocardiographic or blood pressure changes.

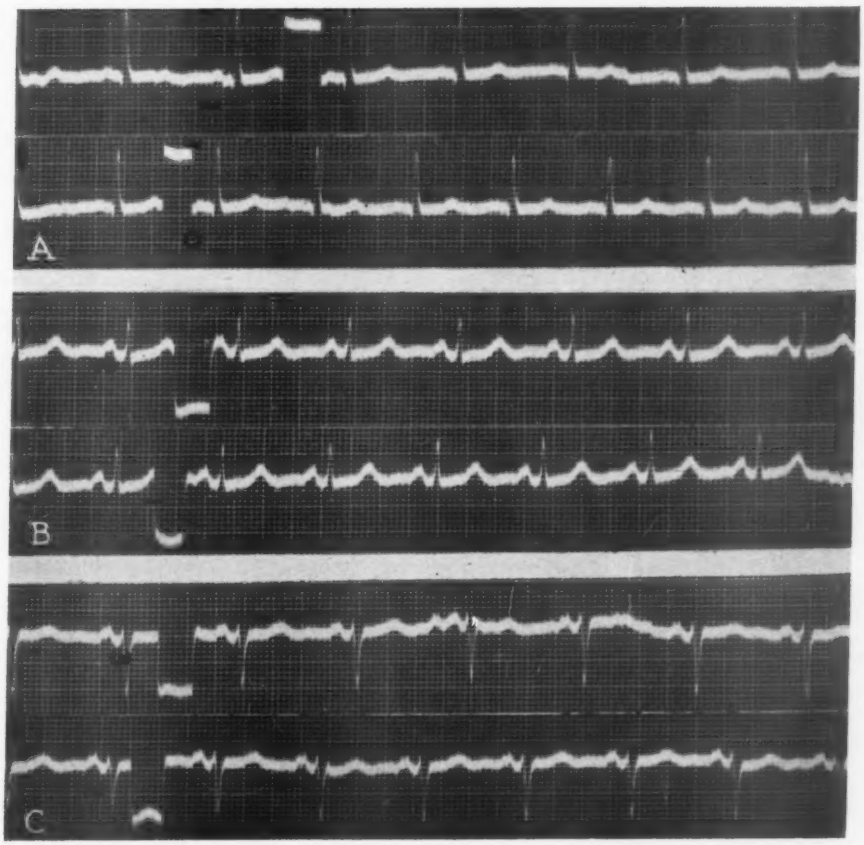

Fig. 6.

CONCLUSIONS

Studies were made of the effects of trichlorethylene on the electrocardiograms of human, canine, and rabbit subjects.

In the canine and rabbit experiments there were marked slowing of the heart rate, ectopic beats, and alterations in the P and T waves. The conducting mechanism and the myocardium were affected.

The administration of a therapeutic dose of trichlorethylene does not produce significant electrocardiographic or blood pressure changes in normal human subjects or in patients with cardiovascular disorders.

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TUMORS OF THE HEART

With a Report of a Primary Fibromyxosarcoma of the Left Auricle and the Pulmonary Vein, Associated With Multiple Tumors of the Mesentery and Alimentary Tract

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Brooklyn, N. Y.

TUMORS of the heart are rare, and their recognition, particularly in the primary form, is exceedingly difficult. They are usually recorded as post-mortem curiosities and, up to the present time, the correct diagnosis has been made in only twenty cases.[1]

The following case is unusual because the diagnosis was made during life and the tumor was found to be associated with other primary tumors.

REPORT OF CASE

A 57-year-old woman was admitted to the medical service of the Israel Zion Hospital Sept. 7, 1941. She stated that she had had "asthma" for twenty years, but gave no history of heart disease, hypertension, or rheumatic fever. She had undergone an appendectomy at 23 years of age, uterine myomectomy at 41 years of age, and cholecystectomy at 45 years of age. She was admitted to the surgical service of this hospital June 14, 1941, for "intestinal obstruction." This was relieved by conservative treatment, and she was discharged July 3, 1941. During her stay in the hospital, she had several attacks of fainting, accompanied by a thready pulse, and, at times, by paroxysms of auricular fibrillation. The electrocardiogram was normal, except for digitalis effect. She was readmitted to the surgical service Aug. 8, 1941, and a large encapsulated tumor was excised. This proved to be a cystic fibromyxosarcoma, apparently arising from the mesentery (vide infra). Histologically, it appeared to be of relatively low-grade malignancy, but of such a type that local recurrence could be expected. The patient made an uneventful recovery and was discharged Aug. 23, 1941. Her fourth and final admission to the hospital was on Sept. 9, 1941. She complained at this time of weakness, increasing cough, wheezing, and dyspnea, accompanied by choking sensations and a sense of precordial heaviness—all of five days' duration.

On admission she had pulmonary edema and auricular fibrillation, both of which disappeared within a few hours. On the following day she could lie flat on her back without dyspnea, and appeared somewhat pale. The heart was not enlarged and the action was regular; the rate was 84. The apex beat was snappy; the pulmonic second sound was louder than the aortic second. There were no murmurs. The neck veins were not distended. The right radial pulse was absent. The blood pressure was 150/80. There were dullness and a moderate number of subcrepitant râles at both bases posteriorly. Slight pretibial edema was also present. The liver and spleen were not enlarged. The admission diagnosis was "anemia, and acute left ventricular failure caused by myocardial disease."

Course.—During the following seventeen days, the patient had several transient attacks of syncope, auricular fibrillation, pulmonary edema, and increasing dyspnea, alternating with periods of comparative well-being. In spite of vigorous treat-

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ment with digitalis and mercurials, she developed increasing pretibial edema and pleural effusion. Except for occasional paroxysms of auricular fibrillation, the electrocardiogram was not remarkable. The circulation time was slightly prolonged (to 18 seconds). These clinical manifestations were definitely indicative of heart failure; nevertheless, it was pointed out that there was no specific evidence of any known cardiac disease to account for them. Therefore, in view of the fact that she was known to have had an abdominal neoplasm, the possibility that tumor invasion of the heart was responsible for the symptoms was now considered.

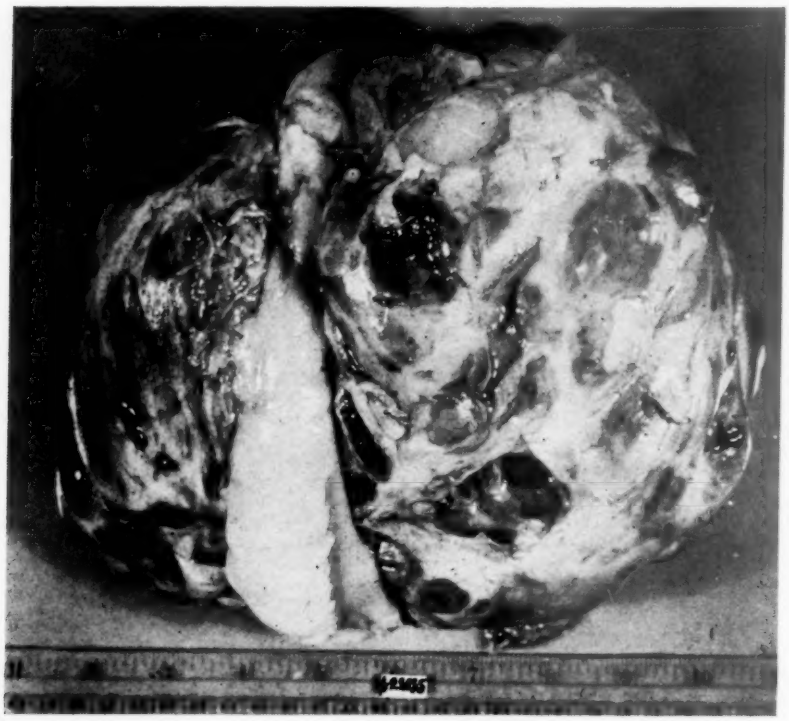

Fig. 1.—Mesenteric tumor, external view. A segment of the intestine can be seen adhering to its mid-portion.

Three days later, a most interesting observation was made. The dyspnea, which was not very noticeable while the patient was reclining, became so intensified when she was placed in the sitting position that she seemed to be choking. Relief occurred only when the patient was again placed flat on her back. The postural change in this symptom was now explained by assuming that she had a pedunculated heart tumor which produced a ball-valve obstruction of the mitral or tricuspid orifice when she was in the upright position. Her condition became progressively worse, and, on the following day, three weeks after admission, she died.

Her temperature ranged between 98 and 99.6° F. The electrocardiogram on September 8 showed a digitalis effect; on September 13, auricular fibrillation; and, on September 24, regular sinus rhythm and P_1 high, and P_2 notched.

Roentgenograms on September 16 showed "shady bases"; on September 26, "fluid in lung bases." The bones and lungs were free from metastasis.

The urine showed traces of albumin, an occasional erythrocyte, a few leucocytes, and casts; the specific gravity was 1.007 to 1.026. The hemoglobin was 50 to 63 per cent; the erythrocyte count, 3,600,000; and the leucocyte count, 6,000 to 11,400, with a normal differential. The blood glucose was 90 to 112 mg. per 100 c.c.; the urea nitrogen, 20 to 25 mg.; and the cholesterol, 240 mg.

Pathologic observations.—The abdominal tumor, which was removed surgically two months before death (Fig. 1), was a huge, football-sized mass weighing 2,070 grams and measuring 23 by 30 by 10 cm. A segment of small intestine was tightly adherent to it and had to be resected with it. The surface was lined by an intact, fibrous capsule, beneath which many semitranslucent cysts were bulging. On cross section (Fig. 2), it was honeycombed with numerous pea- to plum-sized cystic cavities, filled with amber- to ruby-colored serous and semigelatinous myxomatoid fluid which coagulated soon after exposure to the air. The inner lining of the cysts was smooth. The intervening connective tissue stroma was tough but relatively scant in amount.

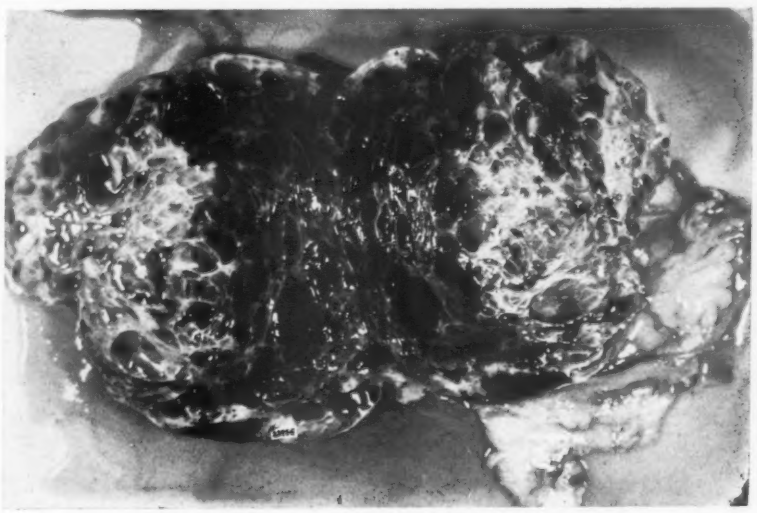

Fig. 2.—Mesenteric tumor, cross section. Note the numerous cysts, in some of which the semitranslucent myxomatous fluid can still be recognized. The thick, viscous, mucoid fluid, which oozed out from the tumor upon sectioning it, can be seen in the background.

Microscopically (Figs. 3 and 4), there was a variety of structures, consisting, in the main, of loose cellular connective tissue. The cells were, for the most part, rather large, pyramidal, stellate, or multipolar, and quite loosely distributed throughout the fine fibrillar stroma. The nuclei usually occupied the wider pole, varried in size, and were ovoid, rounded, or slender and oblong. The chromatin was arranged in fine specks, with occasional nucleoli and a well-defined nuclear membrane. Some of the cells were more sausage-shaped or stellate. The cytoplasm of the cells was abundant and deeply acidophilic; it ended in one wide, rounded process, and one, or several, pointed processes which were given off usually from the end farthest from the nucleus and merged with the intricate network of the matrix. Occasional nuclear hyperchromatism and mitoses were seen. The loose fibrillar and hyaline matrix was frequently divided into innumerable minute, refractile droplets, or bacilloid rods. This was especially seen in the vicinity of, and within, the cavities. Throughout the section there were many cystic cavities of various dimensions, filled with acidophilic granular debris, with

a scant number of mesenchymal cells interspersed. The lining of these cystic cavities was, for the most part, ill defined; their cells were identical and merged with the tumor cells. In places, however, distinct endothelium lined these cysts.

The relative proportion of the cells to the matrix varied. For the most part, the latter predominated; it was a rather loosely knit, fine, fibrillar meshwork which, in places, was pale staining, and myxomatous in appearance. Islands of cartilage cells and osteoid tissue, as well as bone trabeculae, were also seen here and there.

A mucicarmine stain showed a few scattered pinkish patches.

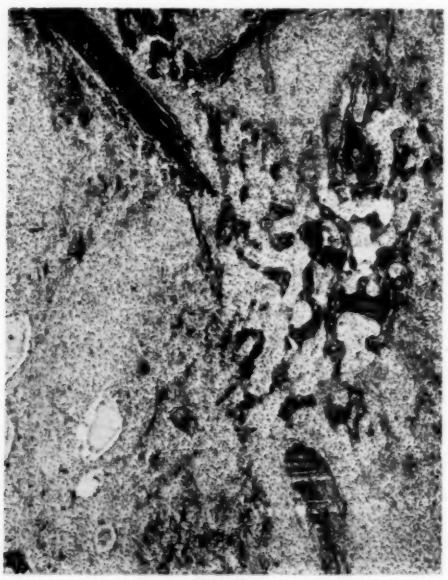

Fig. 3.

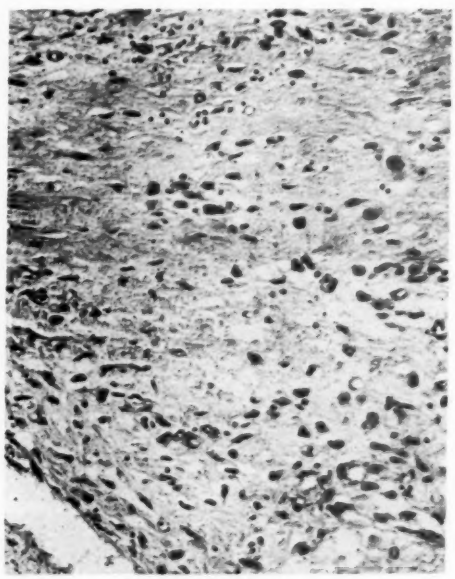

Fig. 4.

Fig. 3.—Low-power photomicrograph of mesenteric tumor, showing patches of myxomatous areas, varying in cellularity, with a number of giant nuclei in the lower half of the field. Five cysts are seen at the lower field. On the right are a number of bone trabeculae with islands of osteoid tissue and cartilage cells. (×25)

Fig. 4.—High-power photomicrograph of one field in Fig. 3, showing pleomorphism of cells and their nuclei. A cystic area is seen at the left lower corner. (×215)

Autopsy (two and one-half hours post mortem).—The body was that of a well-developed, obese, white female of the age of 65 years. The mucous membranes were moderately cyanosed. The abdominal and thoracic organs were in their natural position. The left and right pleural cavities contained 1,200 and 500 c.c. of serohemorrhagic fluid, respectively.

The heart (Figs. 5, 6, and 7) weighed 500 grams and measured 11 by 12 by 4 cm. There was a marked widening in the region of the left auricle, which bulged both anteriorly and posteriorly.

On opening, three polypoid tumor masses were found in the left auricle. The largest and the most anteriorly situated mass was the size of a tangerine, measuring 6.8 by 6.5 by 4 cm. It was situated mainly in the apex of the atrium, arising from its superior aspect. Its anterior and posterior surfaces were flattened, smooth, glistening, pale whitish, and lobulated. The free edge was tongue-shaped and beveled. The attached edge had a broad base 60 mm. in length, which merged imperceptibly with the endocardium. On section, it was hard and woody in some places and semielastic and rubbery in others. The second nodule was the size of a peach. It measured 50 by 30 by 10-20 mm. Its tongue-like free

edge was situated posteriorly to the larger mass, reaching a point 10 mm. from the origin of the third mass. At its right border it extended directly into the upper right pulmonary vein and occluded it completely (Fig. 7). A fresh, friable thrombus, 15 mm. in length, was adherent to the distal end of this nodule within the pulmonary vein. No break in the auricle or vein could be found. The lower branch of the right pulmonary vein contained no tumor, but was compressed externally by the tumor within the adjacent vein and auricle.

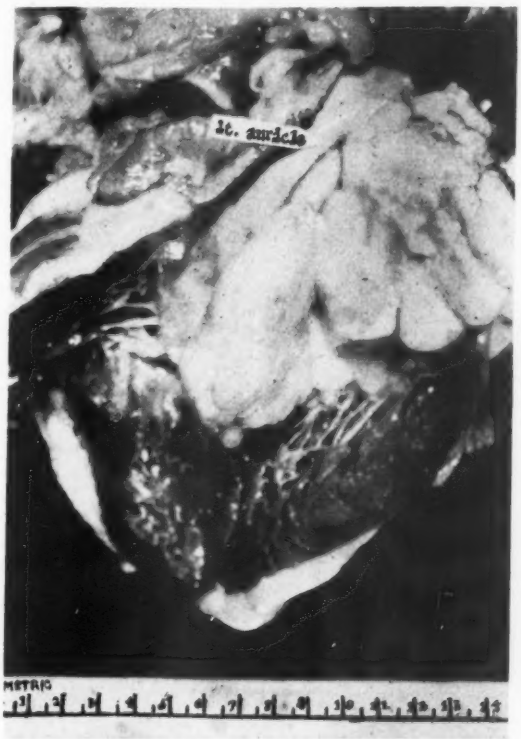

Fig. 5.—Heart, with the auricle, ventricle, and mitral valve exposed. The polypoid tumor can be seen filling the greatly dilated auricle. One tumor nodule extends just beyond the mitral valve.

The third mass was situated in the lowermost portion of the auricle. It measured 50 by 35 by 30 mm. It was attached by a broad base to the endocardium of the interauricular septum near the fossa ovalis, at a point 30 mm. proximal to the free edge of the posterior leaflet of the mitral valve. The foramen ovale was closed. When the heart was held vertically, the largest tumor reached the mitral valve, while the medium-sized tumor entered the mitral ring and spread apart its leaflets. The third tumor extended 15 mm. beyond the free border of the mitral valve, and lay on top of the apices of the papillary muscles.

The mitral valve was widened, measuring 9 cm. in circumference. Its posterior leaflet was slightly thickened, but otherwise it was normal. The left ventricle was small, about 30 mm. in depth. The left auricle was three times its normal size, measuring 11 cm. in its widest diameter, whereas the left ventricle was only 60 mm. wide in its widest portion. The wall of the left ventricle measured 25 mm., and that of the left auricle, 5 to 8 mm., in thickness. The aortic valve

Fig. 6.—Auricular tumor, resting upon the mitral valve, close-up view. In the upper left there is a cross section of one of the nodules, which shows the characteristic glazy or semitranslucent appearance of the tumor.

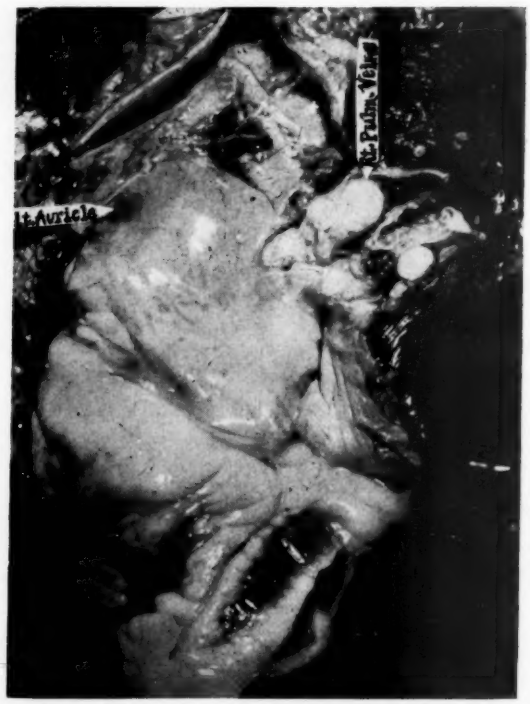

Fig. 7.—Heart, posterior view, showing the markedly dilated left auricle and the invading tumor within the right pulmonary veins.

measured 65 mm. in circumference, and its leaflets showed slight lipoidosis. The right auricle was somewhat dilated. The tricuspid valve measured 10 cm., and the pulmonary valve, 6 cm., in circumference. The wall of the right ventricle was somewhat thickened, measuring 10 to 15 mm. in width.

The aorta showed moderate subintimal lipoidosis. The left lung was atelectatic in places.

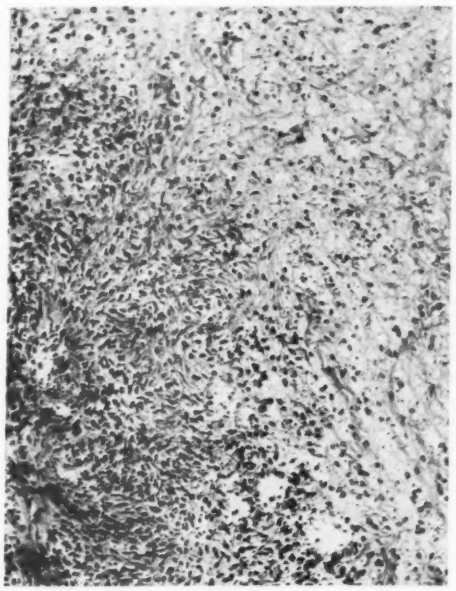

Fig. 8.

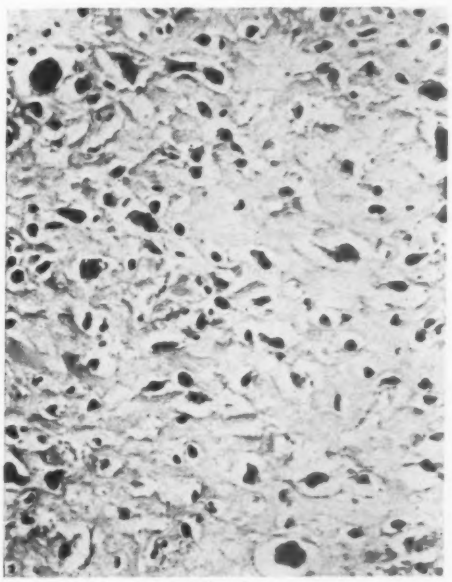

Fig. 9.

Fig. 8.—Medium-power photomicrograph of heart tumor, showing great variation in the histologic picture. The right half is more myxomatous and relatively acellular. The left half is more cellular and fibrous. In the left lower quadrant are seen a number of cells with bizarre shaped and giant nuclei. (×95)

Fig. 9.—High-power photomicrograph of heart tumor, showing the pleomorphism and two mitotic figures in the upper and lower edges. (×250)

Microscopically (Figs. 8, 9, and 10), the auricular tumor was composed of connective tissue cells arranged in whorls of all sizes, as well as in loose aggregates of no distinct pattern. There was great pleomorphism of the cells and their nuclei. The nuclei were rounded, oval, oblong, sausage-shaped, plump, or slender, and many of them were of a bizarre shape. Almost all the cells had one rounded end and another pointed one, ending in one or several acidophilic processes which merged with the intricate network of the collagenous fibrils and the denser fibers of the matrix. A number of bi- or multinucleated cells were also found. The stroma varied in the amount of fibrillar elements; it was deep pink in some areas and loose, pale or faintly staining and myxomatous in others. The relative proportion of cells to stroma varied considerably in different fields.

Within the glazy myxomatous matrix, stellate and comma-shaped cells were seen. Islands of osteoid tissue, cartilage as well as bone, were also found.

The various histologic elements were more clearly brought out in differential stains with Van Gieson, Schmorl, and Mallory's phosphotungstic acid hematoxylin. With mucicarmine, only occasional pinkish areas were found.

The tumor blended imperceptibly with the subendocardial connective tissue layer of the atrium, but nowhere did it invade the myocardium.

In the pulmonary vein (Fig. 11), the tumor obliterated the lumen. The endothelium, however, was more or less intact. The tumor was of the same type as that in the auricle. At the edge of the advancing tumor there was a recent thrombus which showed beginning organization.

Fig. 10.—High-power view of another field of the auricular tumor, showing an almost acellular area, with myxomatous cells and matrix, and with one bone trabecula at the bottom. (×200)

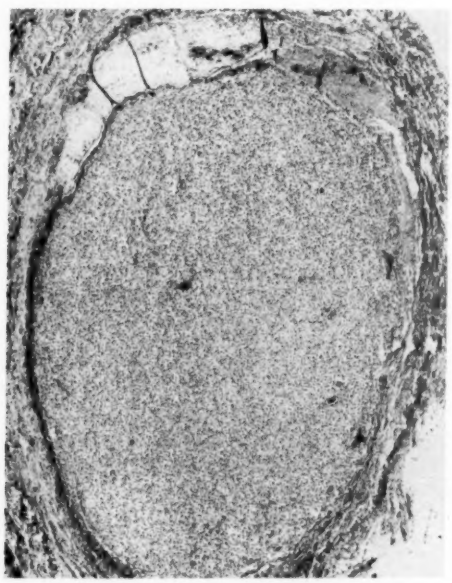

Fig. 11.—Low-power photomicrograph of the pulmonary vein occluded by the tumor. The uniform myxomatous character is more pronounced here. In the upper right corner a fresh hyaline thrombus is seen adhering to the tumor. (×25)

The stomach showed a small diverticulum along the lesser curvature and three pea-sized submucous polyps 2 to 5 mm. in diameter. Microscopically, the latter were made up of bundles of smooth muscle fibers in whorly arrangement, originating from the muscularis and replacing its upper layer.

In the jejunum there was a small mucosal nodule 12 mm. in diameter. Microscopically, it consisted of a miliary submucous nodule composed of whorls of spindle-shaped cells, with large hyperchromatic nuclei. This nodule was ill defined, more invasive, and occupied the mucosa as well as part of the submucosa.

In the rectum there was a cherry-pit-sized nodule 7 mm. in diameter, which, histologically, was an argentaffin or carcinoid tumor such as is not uncommonly found in the intestine and especially in the appendix.

In the uterus multiple leiomyofibromata were found.

The changes in other organs were insignificant.

The Anatomic Diagnoses were primary polypoid fibromyxosarcoma of the left auricle, with direct extension into the right upper pulmonary vein and secondary thrombosis of this vein; pulmonary edema; chronic passive congestion of the liver and spleen; diverticulum of the stomach; multiple submucous leiomyomata of the stomach; miliary submucous leiomyosarcoma of the jejunum; small argentaffin tumor of the rectum; multiple leiomyofibromata of the uterus; encapsulated, cystic, telangiectatic fibromyxosarcoma of the mesentery; and operative enteroanastomosis of the ileum.

COMMENT

The early symptoms in this case were indicative of left ventricular failure; yet no definite cardiac disorder could be discovered to account for it adequately. There was no cardiac enlargement or evidence of disease of the valves, endocardium, myocardium, pericardium, or coronary arteries. This disturbing inconsistency was stressed repeatedly, and therefore, on September 26, nineteen days after admission, it was postulated that the symptoms could be explained by a tumor of the heart, secondary to the pre-existing abdominal neoplasm. Four days later, because of the severe choking sensation induced by the sitting posture, a more definite diagnosis of ball-valve ostial growth was made, which was verified by autopsy. In this way the clinical manifestations could be readily explained. The dyspnea was caused by pulmonary engorgement resulting from obstruction of the blood flow through the pulmonary vein, left auricle, and mitral orifice. The outstanding single feature that led to the diagnosis of ball-valve tumor was the choking sensation produced by the upright posture, which, in turn, caused a more complete occlusion of the mitral orifice. In the reclining position the pedunculated masses were dislodged, with consequent resumption of the circulation. Incomplete mitral obstruction by the tumor accounted for the remainder of the symptoms, which consisted of transient attacks of pulmonary edema, fainting spells, feeble pulse, auricular fibrillation, and the meager evidences of mitral obstruction. The electrocardiogram, except for transient auricular fibrillation and high P waves, was not significant.

Relation of the Heart Tumor to the Mesenteric Tumor.—From the gross appearance alone, it was evident that there could be no direct connection between these two tumors.

The site of origin of each was in common with the usual locations of these respective types of tumor, and by no stretch of imagination could either be conceived of as a metastatic growth of the other. Histologically, however, it must be admitted that there seemed to be a great resemblance between the two, but this relationship was more apparent than real, i.e., it was at best only a generic one, for both were mesoblastic in origin.

Further support for the view that they were independent can be adduced from the fact that there were five other uncommon submucosal tumors: the leiomyomata of the stomach and intestines and argentaffinoma of the rectum, which surely bore no relationship to them. Thus, if there is such a thing as a "tumor diathesis," this patient presents a classical illustration of the phenomenon.

As to the pathogenetic relationship of this or any other myxomatous heart tumor to a thrombus—a view which has been in vogue and cited from time to time since the days of Czapek[2] and Thorel[3-6]—it is mentioned here only to be dismissed. For all the arguments in opposition to such a view which were advanced by Fawcett and Ward[7] and others can, in the light of the above gross and microscopic observations, be applied with equal force in our case as well. It must be concluded, therefore, that these polypoid myxomatous tumors are true and genuine primary neoplasms, and bear no relationship whatsoever to a thrombus. A more plausible view is the one exponded by Ribbert,[19] in 1904, namely, that they arise from isolated rests of embryonal myxomatous tissue along the valves and the endocardium, especially in the vicinity of the foramen ovale. This view can also be applied to the genesis of the large mesenteric tumor in our case.

DISCUSSION AND REVIEW OF LITERATURE

The incidence of tumors of the heart is extremely low. Thorel,[3] in his comprehensive treatise "Pathologie der Kreislauforgane," in 1903, stated that he had not seen a single case of genuine primary tumor of the heart among 3,000 autopsies in Nürnberg within the period from 1894 to 1902. Nevertheless, case reports of such tumors have been appearing in the literature for the last one hundred years. The ratio of primary to secondary growths is given as 1:16. Scott and Garvin[8] found 118 heart tumors among 11,100 consecutive autopsies in which 1,082 general tumors were encountered. Lymburner[9] reported 52 heart tumors in 8,500 autopsies from the Mayo Clinic. Out of 40,000 autopsies, Benjamin[10] reported 0.03 per cent of primary tumors and 0.5 per cent of secondary cardiac neoplasms. In a statistical study of the autopsy material at the Israel Zion Hospital, we have found an incidence of 0.05 per cent for primary tumors of the heart (one in 1,888

consecutive necropsies). Lisa, et al.,[11] recorded 119 cases which were reported in the literature from 1918 to 1941. In this group there were forty-one primary malignant tumors, 90 per cent of which were sarcomas, and forty-seven secondary malignancies, consisting of 50 per cent carcinomas and 25 per cent sarcomas. In this collection, there were thirteen cases which resembled ours in that there was a pedunculated mass in the left auricle which projected into the left ventricle through the mitral orifice.

From a review of the gross and microscopic appearance of the primary tumors of the heart which have been reported to date, it would appear that by far the most common type is the myxoma or the fibromyxosarcoma. Thus, most of the tumors which have been variously regarded as "polypoid fibroma," "spindle cell" sarcoma, giant cell sarcoma, "mixed cell" sarcoma, and simple "sarcomas" appear to belong to this type. It should be recognized that these tumors belong to one specific type, which is almost as distinct as that of fibromyoma of the uterus. All of them exhibit an almost stereotyped characteristic gross appearance and origin, and their histologic pictures are also frequently quite similar. As an example, we may cite our own case, which is almost identical with the one reported by Bacmeister in 1906.[12*]

The sites and methods of invasion of the various tumors are given as follows:[13] In general, any portion of the heart may be involved; primary tumors involve the left side of the heart more frequently. They often arise from the fossa ovalis in the left auricle, forming a pedunculated mass which projects into the left ventricle through the mitral orifice and produces a ball-valve effect. Metastatic tumors occur more often in the right side of the heart, and the primary lesion may be situated in any organ of the body. Carcinoma of the breast and bronchus account for 48 per cent of cardiac metastases. The pericardium is usually invaded by mesothelioma and granuloma, the myocardium, by sarcoma, fibrosarcoma, and rhabdomyoma, and the endocardium, by myxoma and polypoid fibroma. There are three methods of spread of secondary tumors: (a) direct invasion, or extension from adjacent organs, as from the bronchi, lungs, mediastinum, or pleura; (b) infiltration by systemic diseases, as in Hodgkin's disease, leucemia, or sarcoid; (c) lymphogenous or hematogenous invasion from other organs, such as the breast, bronchi, or thyroid, and from the gastrointestinal, genitourinary, and biliary tracts.

The clinical manifestations are variable, and depend upon the size and location of the tumors. Pericardial involvement is suggested by

*Haythorn, Ray and Wolff,[13] quoting Thorel,[3] state that Bacmeister "seemed to have been the first to postulate that the tumors (fibromyxomas) began as organizing thrombi and underwent metaplasia into true neoplastic growths." Bacmeister's original article, however, does not contain such a statement. On the contrary, Bacmeister believed that his tumor was a genuine myxoma and "of congenital origin." Thorel,[3] on the other hand, although Bacmeister's tumor "showed histologically a typical myxomatous structure," doubted whether it was a myxoma, and thought that it was "an edematous ball thrombus" because it was not "subjected to the specific stain for mucus."

a friction rub, tamponade, or sanguinous effusion causing progressive cardiac enlargement, and fluoroscopic examination may reveal a rigid, nonpulsating cardiac border because of tumor infiltration. The electrocardiogram may show the R-T segment changes which are characteristic of pericarditis.

Myocardial invasion may be manifested by congestive failure, various arrythmias, heart block, or auricular fibrillation. Encroachment on the coronary arteries will usually cause coronary insufficiency, with consequent myocardial anoxia, followed by angina and characteristic R-T-T changes.

Endocardial tumors can produce embolism, or bizarre murmurs if the valves are affected, or intermittent occlusion of the cardiac orifices. In a considerable number of instances, a pedunculated tumor interfered with the cardiac dynamics. If it projects into the mitral ostium, as it did in our case, it causes retardation and narrowing of the blood stream, producing signs of mitral stenaosis. As the tumor continues to grow, it may produce a ball-valve mitral syndrome which consists of mitral stenosis, transient changes in the pulse and peripheral circulation, paroxysmal auricular fibrillation, and a variability of symptoms with postural changes (Abramson[15]). Moderate mitral obstruction may cause fainting and accentuation of dyspnea which are relieved by a change in the posture of the patient. More complete mitral obstruction may be responsible for peripheral circulatory disturbances which are characterized by "cadaveric coldness of all four extremities and the tip of the nose, sometimes proceeding to ischemic gangrene, and associated with intense cyanosis and with feeble or absent pulse" (Fishberg[16]). Sudden death occurs in 29 per cent of these cases.

The possibility of a cardiac tumor is hardly ever entertained, but with the additional knowledge derived from an ever-increasing literature on the subject, the condition should be more often considered. Metastatic tumor of the heart was first diagnosed by Roesler,[17] in 1924, and ten years later the first correct diagnosis of primary tumor of the heart was made in this country by Barnes, Beaver, and Snell.[18] The recognition of a primary heart tumor is extremely difficult, but the presence of a secondary tumor should be suspected when unexplained cardiac abnormalities develop after or during the course of neoplastic disease elsewhere in the body. The absence of any known types of heart disease to account for the presenting cardiac manifestations is very suggestive. Mitral stenosis of unknown cause occurs in 50 per cent of the cases, and, when accompanied by unexplained dyspnea and fainting spells which are influenced by postural changes, it offers an important diagnostic feature. The dyspnea is often unyielding and wholly out of proportion to the cardiac abnormalities. It may be a prominent symptom and it often occurs without orthopnea, which is unlike that of ordinary types of heart failure. Signs of ball-valve effects on the cardiac orifices, with or without postural changes, are also highly significant.

The sudden onset of transient arrythmia or intractable heart failure, after known malignancy, is of valuable aid. Other helpful signs consist of bizarre, contradictory combinations, such as severe dyspnea without obvious cause which remains refractory to treatment, or mitral stenosis accompanied by peripheral circulatory disturbances. The electrocardiogram is not characteristic, but the transient nature of the various arrythmias may be significant. Of more valuable aid in the diagnosis is the development of recurrent, unexplained, hemorrhagic pericardial effusion, or progressive, bizarre cardiac enlargement. Fluoroscopic examination may reveal rigidity of heart border, with absence of pulsation, as a result of tumorous infiltration of the epicardium. Positive evidence of the existence of a cardiac neoplasm consists, however, in the recovery of tumor cells, either from aspirated pericardial fluid or from a metastatic focus.

SUMMARY

A case of a primary cardiac tumor, in which the diagnosis was made during life and confirmed by autopsy, is presented. It was associated with multiple primary tumors in other organs. The pathogenesis, clinical manifestations, and diagnostic features of neoplasms of the heart are discussed.

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THE SIGNIFICANCE OF VASCULAR HYPERREACTION AS MEASURED BY THE COLD-PRESSOR TEST

Observations on 200 Normal Subjects Over the Age of 40

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According to Hines and Brown,[1] essential hypertension is a syndrome which develops upon the soil of a hyperreactive vasomotor system. Subjects with vascular hypertonicity and normal blood pressure are regarded by the authors as candidates for the disease. In support of this view, Hines[2] has found a high incidence of hypertensive cardiovascular disease in the families of normal subjects who exhibit a hyperreactive response to the cold-pressor test. The fate of the hyperreactor, according to the author,[3] is reflected by the observation that 38 per cent of twenty-one originally normal hyperreactors developed hypertension within six years, as compared to none of the normal hyporeactors. In line with this apparent trend is the author's statement that the incidence of hyperreaction in children approximates the combined incidence of hyperreaction and hypertension among adults.

Although most authors have reported data in accord with this concept, the observations of Pickering and Kissin[4] did not confirm the view that a relatively high rise of blood pressure in response to a cold stimulus is peculiar to persons with potential or established hypertension. They noted that nine normal subjects with an average age of 53 years showed an average response similar to that of twelve hypertensive patients with an average age of 54 years. The small number of cases studied, however, does not permit acceptance of the authors' conclusions. The investigations of Chesley and Chesley,[5] and Feldt and Wenstrand,[6] on the other hand, seriously open to question the significance of a hyperreactive response in the development of essential hypertension. These authors, in studies on a large number of cases, found no relationship between the response to the cold-pressor test and a family history of hypertensive cardiovascular disease.

Further contradiction of the theory that hyperreaction indicates a predisposition to essential hypertension seems apparent from the original observations of Hines and Brown. They noted, paradoxically, that in the subjects with normal blood pressure there was an appreciable increase in the range of reaction in the latter decades of life. This is not in harmony with the authors' statement that "the response of the blood pressure is characteristic for the individual and probably remains so throughout life." Furthermore, calculations from the data in their tables would show that 35 per cent of normal subjects over the

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age of 40 years are hyperreactors, as compared to only 23 per cent under that age. Obviously, if hyperresponse in youth means hypertension later in life, one should expect to find a decreasing incidence of normal hyperreactors with increasing age. Yates and Wood[7] did not find this to be the case, but their series included only thirty-four subjects over the age of 40 years, and thirteen of 50 years or older. They did not, however, observe a greater response in older subjects than in young ones, as reported by Pickering and Kissin.

Hines and Brown[8] have attributed the increased incidence of normal hyperreactors among the older subjects of their series to a latent or subclinical form of essential hypertension. A study of fifty such persons between the ages of 34 and 65 years revealed no previous history of elevated blood pressure, although a hypertensive sclerosis of the retinal arterioles of Grade I or more was found in all instances. Some of their subjects who were followed for years did not show evidence of an elevated blood pressure. Nevertheless, a family history of hypertensive cardiovascular disease was found in 82 per cent of these hyperreactors, as compared with only 14 per cent of a group of hyporeactors. From the various studies of these authors, therefore, it would seem that hyperresponse at any age is associated with a positive family history in over 80 per cent of the cases. The present paper will attempt to show that this view is untenable for older persons, as indicated by clinical and statistical considerations.

The following series of observations on two hundred normal male subjects over the age of 40 years is being presented because it fails to support the idea that "vascular hyperreactivity" is a significant factor in the development of essential hypertension.

TECHNIQUE OF THE COLD-PRESSOR TEST

The procedure as outlined by Hines and Brown was followed throughout. The subject remained recumbent in a quiet room, and blood pressure readings were taken over variable periods until a basal level was reached. The rest period was twenty to thirty minutes, and, usually, four to five readings were made. The sphygmomanometer cuff remained on the arm during the whole procedure, and, when the lowest level of blood pressure was reached, the free hand was placed in a basin of water at a temperature of 4° C. The hand was kept immersed to a level just above the wrist for sixty seconds. The blood pressure was measured at thirty and sixty seconds.

The response is recorded as the difference between the basal level and the maximum reading. Using the authors' criteria, subjects whose response exceeded 20 mm., systolic, and 15 mm., diastolic, were called hyperreactors. Those whose response did not exceed these figures were designated as hyporeactors.

SUBJECTS OF TEST AND RESULTS

The test was performed on two hundred merchant seamen with normal blood pressure. All were ambulant hospital patients who had been admitted for a variety of minor ailments unrelated to the cardiovascular system. The blood pressure was not accepted as normal unless all

previous readings were below 145 mm., systolic, and 95 mm., diastolic. Many of the subjects knew approximately what their pressure was because of former recordings made prior to boarding ships. An appreciable percentage of them had had one or more previous admissions to this hospital over a period of years, and the available data served as an additional check on the accepted levels of pressure. The ages ranged from 40 to 69 years, and the average was 56 years. The results are summarized in Table I. The average response to the cold-pressor test was 21.4 mm., systolic, and 15.0 mm., diastolic. There were 82 hyperreactors (41 per cent), with an average response of 32.0 mm., systolic, and 21.5 mm., diastolic. Among 118 hyporeactors (59 per cent) the average response was 14.0 mm., systolic, and 10.4 mm., diastolic.

TABLE I

SUMMARY OF RESULTS WITH COLD-PRESSOR TEST

	SUBJECTS		AVERAGE RISE OF BLOOD PRESSURE IN MILLIMETERS OF MERCURY	
	NUMBER	PERCENTAGE	SYSTOLIC	DIASTOLIC
Entire Group	200	100	21.4	15.0
Hyperreactors	82	41	32.0	21.5
Hyporeactors	118	59	14.0	10.4

TABLE II

AGE AND AVERAGE RESPONSE TO THE COLD-PRESSOR TEST

AGE (YEARS)	ENTIRE AGE GROUP		HYPOREACTORS		HYPERREACTORS	
	SYSTOLIC RISE	DIASTOLIC RISE	SYSTOLIC RISE	DIASTOLIC RISE	SYSTOLIC RISE	DIASTOLIC RISE
40-49	14.0	10.0	10.6	7.5	24.6	18.0
50-59	22.6	16.6	15.0	11.8	33.0	23.3
60-69	27.6	18.1	17.5	13.2	35.5	21.9

Table II shows the effect of age upon the response to the cold-pressor test. For the entire group the average systolic elevation rose from 14 mm. in the fifth decade to 27.6 mm. in the seventh decade. The average diastolic response increased from 10.0 mm. to 18.1 mm. in the same interval. Among the hyporeactors the average systolic response increased from 10.6 mm. to 17.5 mm., whereas the average diastolic response increased from 7.5 mm. to 13.2 mm. in the age groups studied. In the hyperreactor group the average systolic response increased from 24.6 mm. in the fifth decade to 35.5 mm. in the seventh decade. The average diastolic response, on the other hand, increased from 18.0 mm. to 23.5 mm., and then showed a fall to 21.9 mm. with succeeding decades.

Chart I shows the effect of age upon the incidence of hyperreaction to the cold-pressor test. Of sixty-two subjects between the ages of 40 and 49 years, 24.2 per cent were hyperreactors. There were eighty-one subjects between the ages of 50 and 59 years, and, of these, 43.2 per

cent were hyperreactors. Between the ages of 60 and 69 years, 56.1 per cent of fifty-seven subjects showed hyperreaction to the cold-pressor test.

TABLE III

COMPARISON OF FAMILY HISTORY OF HYPERREACTORS AND HYPOREACTORS

SUBJECTS		POSITIVE FAMILY HISTORY OF HYPERTENSIVE CARDIOVASCULAR DISEASE	
	NUMBER	NUMBER	PER CENT
Entire Group	200	53	26.5
Hyperreactors	82	23	28.0
Hyporeactors	118	30	25.4

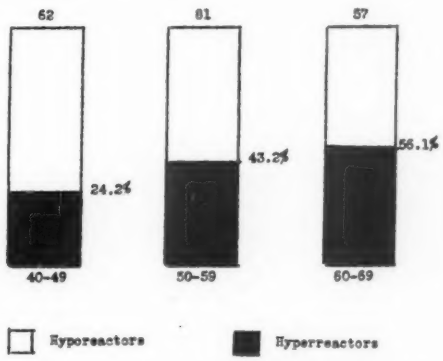

Chart I.—Age and hyperreaction to the cold-pressor test.

In eliciting the family histories, the same standards were applied in all instances, regardless of the cold-pressor response. The state of health, if living, and the cause of death, if deceased, of each parent and each sibling were noted. The subjects were specifically asked if their parents, brothers, or sisters were known to have, or to have had, elevated blood pressure, heart disease, or apoplexy. Only the instances of hypertension or of diseases considered to be the result of hypertension were accepted. Doubtful cases were not included in the study, but their addition would not alter the results because the proportion among hyporeactors and hyperreactors was relatively the same. Table III shows that the response to the cold-pressor test was not related to the family history in this series. Fifty-three subjects, or 26.5 per cent of the entire group, gave a family history of one or more instances of hypertensive cardiovascular disease when parents and siblings were counted. Twenty-three (28.0 per cent) hyperreactors and thirty (25.4 per cent) hyporeactors had such a family history. These figures are greatly at variance with those of Hines, but are in close agreement with the observations of Feldt and Wenstrand.

DISCUSSION

The concept advanced by Hines and Brown assumes that: (1) the cold-pressor response is characteristic for the individual throughout

life, and (2) hyperresponse to the test indicates a predisposition to essential hypertension. If these hypotheses are true, static studies of various age groups should reveal: (1) a decrease in the incidence of normal hyperreactors with advancing age, and (2) an incidence of hyperresponse in children which approximates the combined incidence of hyperresponse and hypertension in adults. Neither of these, however, has been established. The present study indicates a rise in the incidence of hyperresponse from 24.2 per cent in the fifth decade to 56.1 per cent in the seventh decade. The tables of Hines and Brown reveal (by inference) a similar trend with age; 23 per cent were hyperreactors under the age of 40 years, whereas 35 per cent showed a hyperreactive response over that age. The observations of Feldt and Wenstrand were of the same order. Available data, therefore, indicate an appreciable rise, rather than the anticipated fall, in the incidence of hyperresponse with advancing age.

Secondly, since Hines[9] found that 18 per cent of school children are hyperreactors, it is to be expected that the combined incidence of hyperreaction and hypertension in adults will approximate this figure. A study of the levels of blood pressure among aged seamen[10] revealed, for the age group 60 to 69 years, that 60 per cent had normal pressure, 19 per cent had diastolic hypertension, and the remainder were arteriosclerotic subjects with systolic hypertension. Since 56.1 per cent of the normals in the present study were hyperreactors, the latter would represent 33.7 per cent of this age group comprising all levels of blood pressure. In other words, if we assume that arteriosclerotic persons are all hyporeactors, as reported by Hines and Brown, then, in these subjects between the ages of 60 to 69 years, there would be 33.7 per cent normal hyperreactors and 19 per cent hypertensives. The combined incidence would be 52.7 per cent, a figure almost three times the incidence of hyperreaction in the school children previously mentioned. The fact that many of these elderly hyperreactors may be subclinical hypertensives, as alleged by Hines, would not alter the situation, for the combined incidence would still be unchanged. Although the racial and environmental factors in the school children differ from those in the seamen, it is felt that this source of error cannot materially affect the final deductions.

These observations, therefore, seem to offer serious contradiction to the original assumptions of Hines and Brown. Furthermore, inasmuch as the combined incidence of hyperresponse and hypertension in old age far exceeds that of hyperresponse in childhood, the conclusions of Hines regarding family history do not seem valid. This author has stated that "a positive family history of hypertensive cardiovascular disease is 4 to 5 times as frequent among individuals who have hypertension or who are hyperreactors to a standard stimulus test, than it is among individuals who react normally to the test." Since the author noted a positive family history as frequently among elderly hyper-

reactors as among young ones, it would have to be concluded that, in advanced age, a greater percentage of persons belong to hypertensive families than in childhood—a deduction which is contrary to clinical and statistical experience. The present study on subjects over the age of 40 years, furthermore, has shown no relationship between the nature of the cold-pressor response and the family history of hypertensive cardiovascular disease.

The cause of the rising incidence of hyperresponse in successively older groups seems apparent from a consideration of Table II. It is seen that there is not only an increase in the average response of hyperreactors with advancing years, but also an appreciable rise in the average response of hyporeactors. Consequently, it would appear that a hyporeactor at 40 years might become a hyperreactor at 60 years. Since immersion of the hand in ice water for one minute actually produces pain, it seems likely that the older subject will respond with a greater rise in pressure than the younger one whose threshold for pain and vasomotor stability are undoubtedly greater. These data are at variance with those of Hines, who found no significant change in the range of reaction in hyporeactors with advancing years.

Because of the supposed specificity of hyperresponse with respect to hypertension, the use of the cold-pressor test has been advocated as a diagnostic aid in the recognition of latent hypertension.[11, 12] It has been stated that a hyperresponse to the test in the presence of cardiac failure and normal blood pressure is evidence of previous hypertension which is temporarily latent. When it is realized that perhaps 45 to 50 per cent of normal subjects over the age of 50 years show a hyperreactive response to this test, its limitations as a diagnostic method in older persons seem evident.

Although the significance of vascular hyperreaction cannot be fully evaluated until further time has elapsed, the results of this study appear to indicate that hyperresponse in normal, middle-aged, and elderly subjects is unrelated to hypertension.

CONCLUSIONS

An analysis of the cold-pressor response in two hundred normal male subjects between the ages of 40 and 69 years revealed that:

1. Forty-one per cent of the entire group were hyperreactors to the stimulus of cold.

2. The incidence of hyperresponse, contrary to theory, increased, with advancing age, from 24.2 per cent in the 40- to 49-year group, to 56.1 per cent in the 60- to 69-year group.

3. The average response of both hyporeactors and hyperreactors increased with age. Consequently, a hyporeactor at 40 years might become a hyperreactor at 60 years. The increased response was attributed to changes in the threshold for pain and increasing vasomotor lability with succeeding decades.

4. There is no support for the view that the cold-pressor response is characteristic for the individual throughout life.

5. The combined incidence of hyperresponse and hypertension in the subjects 60 to 69 years of age was almost three times the incidence of hyperresponse in the school children observed by Hines. The fact that elderly hyperreactors may actually be latent hypertensives would not influence this comparison.

6. There was no relationship between hyperresponse and a positive family history of hypertensive cardiovascular disease.

7. The high incidence of hyperresponse in normal subjects over the age of 50 renders the test unreliable in the diagnosis of latent hypertension, associated with congestive failure, in this group.

8. Hyperresponse among normal subjects in the later decades of life is unrelated to essential hypertension.

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Clinical Reports

STAPHYLOCOCCUS AUREUS SUBACUTE BACTERIAL ENDOCARDITIS SUPERIMPOSED ON A CONGENITAL HEART LESION, WITH RECOVERY

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THE usually fatal outcome of subacute bacterial endocarditis makes noteworthy all reports of recovery from this condition. A case is presented of subacute bacterial endocarditis due to a *Staphylococcus aureus* infection of a congenitally patent interventricular septum (Roger's disease); the patient was followed for four years after recovery.

CASE REPORT

Los Angeles County Hospital Permanent File No. 108-957. P. B., a single, 18-year-old white girl, was admitted to the hospital for the second time, Aug. 25, 1937, with the complaint of chills and fever of two weeks' duration. Pain in the lower part of the right hemithorax, aggravated by respiration, had also been noted for two days.

The past history was essentially negative, except that she was known to have had "heart trouble" since birth. The first hospital entry, at the age of 11, May 26, 1930, was for study of the heart, although the patient had no cardiac complaints. At this time it was noted that the patient had had heart disease since birth, and had not been expected to survive infancy. No definite information was obtained as to whether or not she had been a "blue baby." Physical examination at this time revealed a well-developed girl who weighed 67½ pounds and was 52½ inches tall. The heart was noted to be enlarged transversely. There was a harsh, blowing, systolic murmur which was heard best at the third left intercostal space, was transmitted along the left sternal border, and was associated with a marked systolic thrill. The fingers were clubbed. A diagnosis of congenital defect of the interventricular septum was made. The only illnesses which the patient had had were measles and mumps as a child. The system history gave no significant information. The family history was noncontributory.

Physical Examination.—The patient was a well-developed young girl who was cyanotic and appeared acutely ill. Her temperature was 103.2° F.; her pulse rate, 116; her respiratory rate, 32; and her blood pressure, not recorded on entry, was later 115/80. The tonsils were moderately enlarged and the pharynx appeared slightly injected. A few small lymph nodes were palpable in the neck. The lungs showed dullness on percussion, with diminished breath sounds at the right base. A few moist râles were heard in this area and in the right axilla. The heart was enlarged, with the angle of cardiac dullness 1 to 2 cm. lateral to the left mid-

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clavicular line. The apex impulse was located in the fifth left intercostal space in the midclavicular line. A systolic thrill was palpable in the fourth intercostal space at the left sternal border. There was a harsh systolic murmur at the apex, obliterating the first sound. A systolic murmur was heard all over the precordium and in the left axilla. The liver and spleen were not felt. No masses were felt in the abdomen. There was slight clubbing of the fingers. The reflexes were normal. Pelvic and rectal examinations were not done.

Laboratory Examination.—(See Table I for routine laboratory studies and blood cultures, Fig. 2 for electrocardiograms, and Fig. 3 for chest roentgenograms.)

Progress and Treatment.—See Table II for details of treatment, and Fig. 1 for temperature curve correlated with treatment.

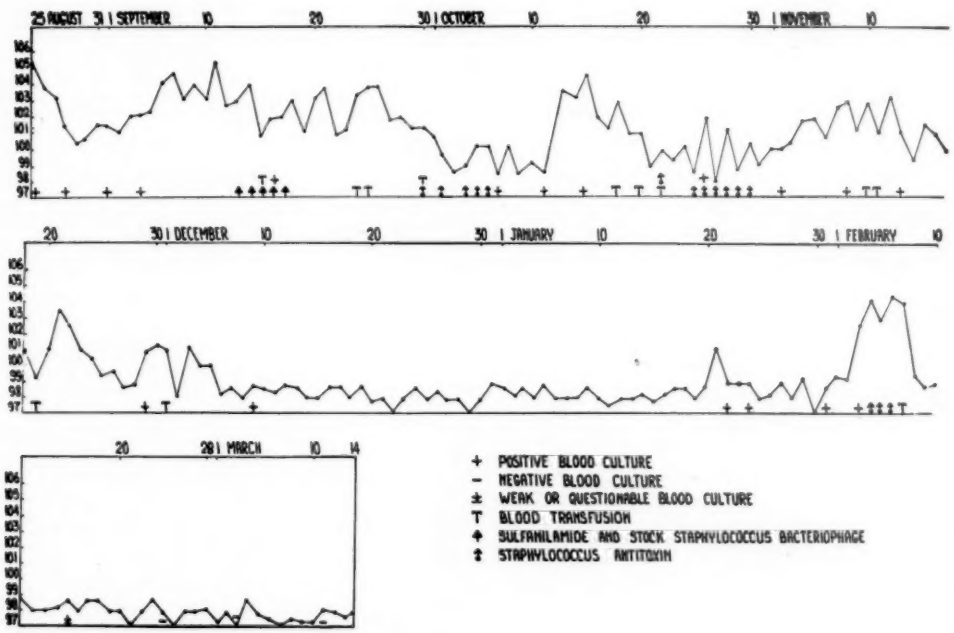


Fig. 1.

Course.—With the repeatedly positive blood cultures for *Staphylococcus aureus*, the cardiac abnormalities, and the febrile course, the diagnosis of staphyococcus endocarditis and a congenital septal defect appeared established. The illness divided itself into four periods:

1. Febrile period: Aug. 11, 1937, to Dec. 8, 1937. (Received two courses of staphylococcus antitoxin.)

2. Quiescent period, with normal temperature: Dec. 8, 1937, to Jan. 20, 1938. (No specific treatment.)

3. Two periods of fever: Jan. 20, 1938, to Feb. 8, 1938. (One course of staphylococcus antitoxin.)

4. Convalescent period, with normal temperature: Feb. 8, 1938, to July 7, 1938. (No specific treatment.)

During the first period, the patient had a high fever, appeared acutely ill at all times, and had repeated chills. Although no petechiae were noted on entry, definite petechiae were seen, a few days after entry, on the left hand and in the right conjunctiva. Jaundice was first noticed Sept. 10, 1937, before any therapy was

TABLE I

LABORATORY DATA

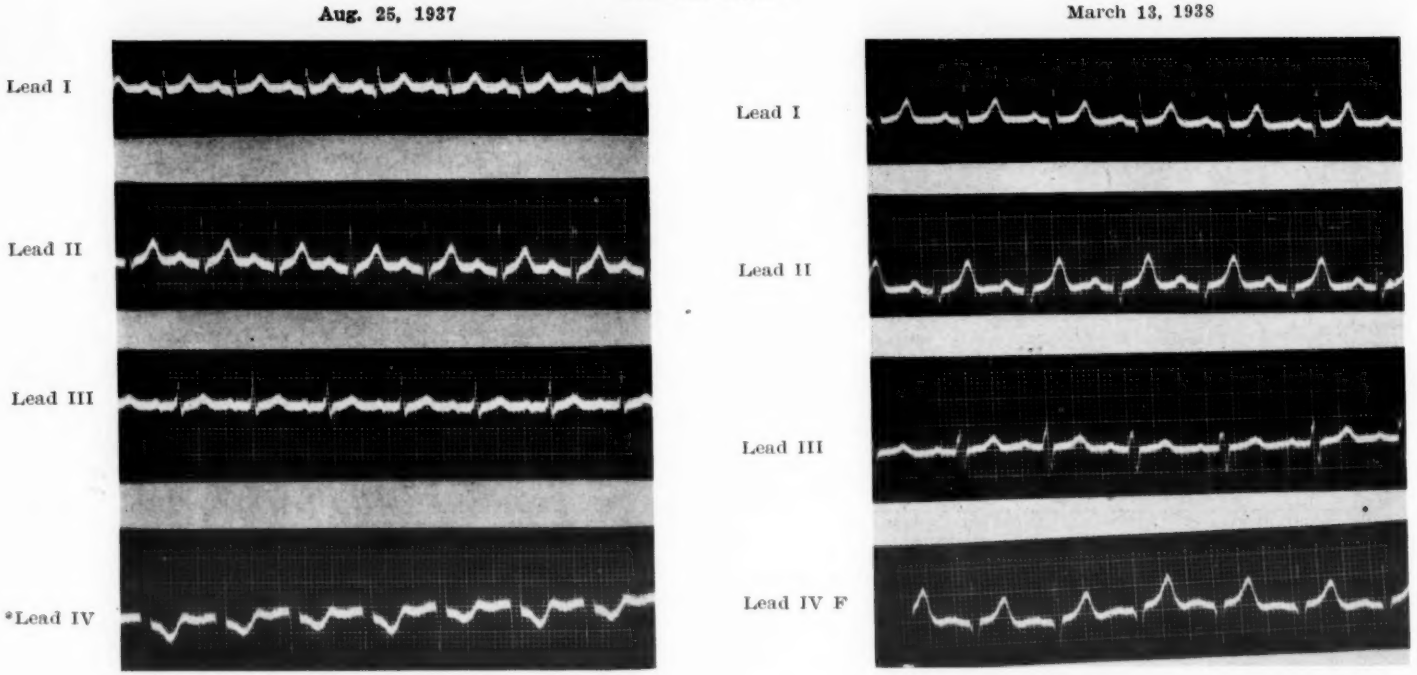
DATE	HGB. % (SAHLI)	R.B.C. IN MILLIONS	W.B.C. IN THOUSANDS	DIFF. COUNT	URINE	BLOOD CULTURES	MISCELLANEOUS
8/25/37	85	4.2	14.6	P 64	Negative	Positive cultures for *Staphylococcus aureus* on: 8/25/37; 8/28/37; 9/1/37; 9/4/37; 9/13/37; 10/7/37;	Widal and undulant fever agglutinations negative
8/29/37							
9/ 9/37					No albumen. Microscopic: 1-2 W.B.C. per high field. Few R.B.C.; Rare casts	10/11/37; 10/14/37; 10/26/37; 11/2/37; 11/8/37; 11/13/37; 11/29/37; 12/9/37; 1/22/38; 1/24/38; 1/31/38; 2/3/38; 2/15/38;	Blood Wassermann and Kahn negative Pleural fluid: no growth
9/13/37	80	4.3	14.2	P 72			
9/21/37						few staph. on direct smear from culture.	Icterus index 57.6. Prompt Van den Bergh 4.5 mg. bilirubin
10/17/37	78	3.85					
11/17/37	80	4.01	8.35	P 68		No growth on subcultures	
12/ 1/37	85	4.87	16.4	P 68			
2/ 2/38	75	3.0	7.35				
2/10/38	84	3.5	7.3	P 50		Negative cultures on: 2/24/38; 3/3/38; 3/11/38; 3/16/38; 3/26/38; 3/29/38	
4/ 7/38	13.6 grams	4.01	6.4	P 59		4/1/38, plate: 1 colony of *Staph. aureus;* broth: no growth 4/11/38, negative 4/25/38, doubtful, gram-negative bacillus 5/2/38, negative 5/16/38, 1 colony of staph. in 1 c.c. plate culture. 6/22/38, negative. 7/22/38, diphtheroid bacillus 8/19/38, negative	Sedimentation rate 12 mm./hr.

started. By September 21, the icterus index was 57.6 units. The jaundice had disappeared by Nov. 17, 1937. When positive blood cultures for the *Staphylococcus aureus* were obtained, an attempt was made, without success, to obtain a specific bacteriophage. A stock staphylococcus bacteriophage and sulfanilamide were tried, without any effect on the clinical appearance or the temperature. Staphylococcus antitoxin (Lederle) was then tried in conjunction with repeated, small blood transfusions. With practically every dose of antitoxin the patient had chills, and on several occasions developed urticaria and joint pains. Many of the transfusions of citrated blood were also accompanied by chills. There appeared to be improvement after the antitoxin, although fever recurred and the blood cultures remained positive.

In the second period, Dec. 8, 1937, to Jan. 20, 1938, the patient appeared slightly improved. No definite embolic phenomena were noted, although the blood cultures remained positive.

Fig. 2.

Electrocardiograms



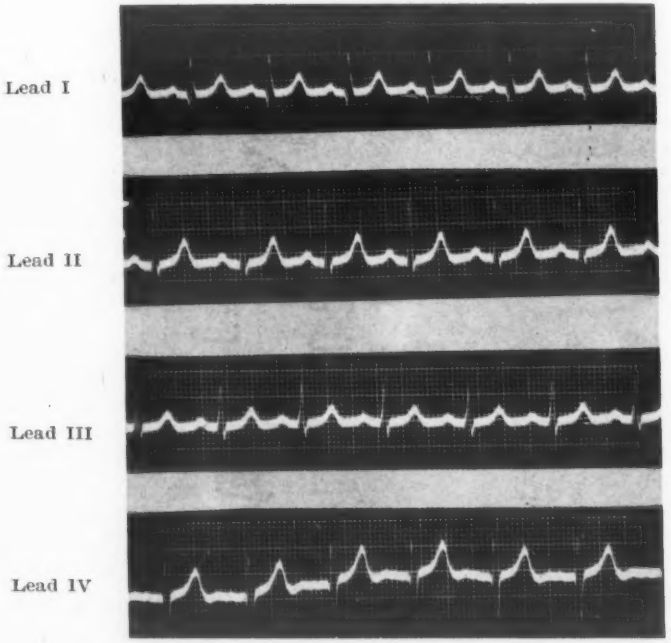
Heart rate — 120/min.
Sinus tachycardia.
P-R interval — 0.17 second.
No deviation of electrical axis.
QRS low amplitude and slurred in Leads I and III.
*Lead IV: T wave diphasic.

Heart rate — 105/min.
Sinus arrhythmia.
P-R interval — 0.16 second.
A deep S wave Lead III.
Left axis deviation.

*Lead IV in this tracing old precordial lead—right arm electrode on apex, and left leg electrode on left leg. All other Fourth Leads are IV F type.

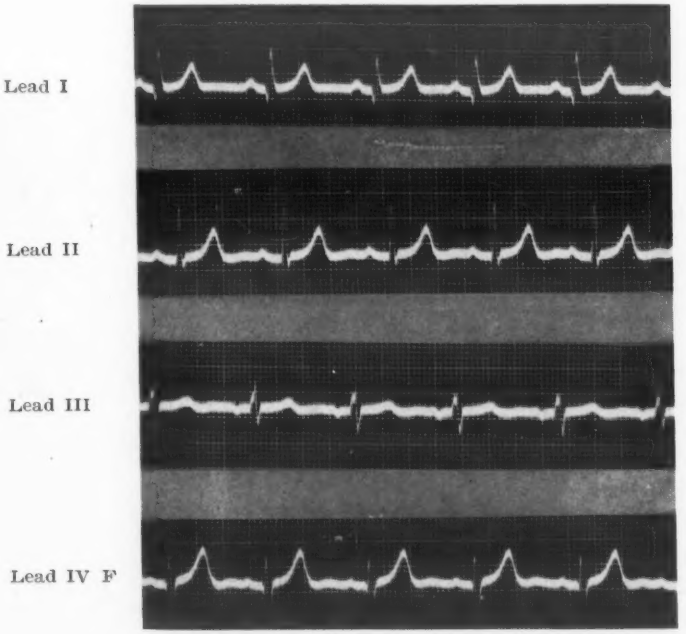
Fig. 2.—Cont'd
Electrocardiograms

June 21, 1938



Heart rate — 92/min.
Slight sinus arrhythmia.
P-R interval — 0.17.
Well-defined Q wave — Lead I.
Some slurring of QRS in Leads I and III.
No significant T-wave changes.

Aug. 7, 1938

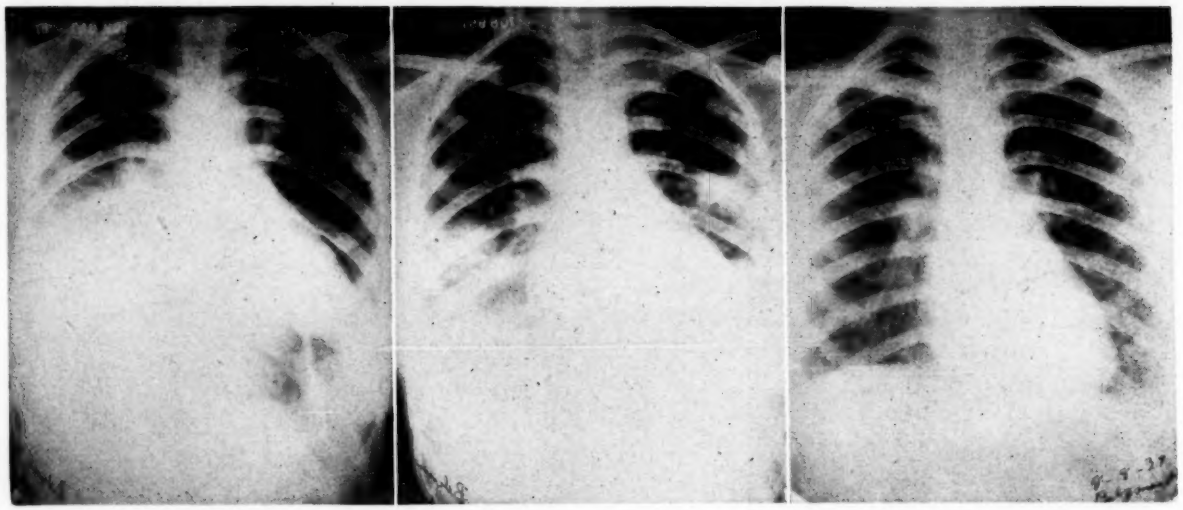


Heart rate — 80/min.
Sinus arrhythmia.
P-R interval — 0.2 second.
QRS interval — 0.06 second.
Left axis deviation.
QRS small and slurred in Leads I and III.
Prominent Q in Lead I. T upright in standard leads; large in Leads I and II. RT_1 is depressed. Low voltaged QRS Lead IV F. T wave in Lead IV F upright and large.

Fig. 3.

Chest Roentgenograms

Aug. 26, 1937	Sept. 22, 1937	Aug. 8, 1939



Heart definitely enlarged to about twice its normal size, with a mitral form. The left costophrenic sulcus is not clearly seen, apparently because of a small pleural fluid collection. The right base is filled with hazy, homogeneous density which is apparently parenchymal in location and may represent a pneumonitis surrounding a septic embolus. Because of the absence of the costophrenic sulcus, at least part of the abnormal density must be assumed to be caused by a pleural fluid collection.

Since examination of Aug. 26, 1937, there has been marked decrease in the density at the right base. However, there is still some hazy opacity in this region and, in addition, a localized zone of hazy density in the left midlung field and at the left base.

Orthocardiogram: Cardiac silhouette bulbous and at upper limits of normal in size. There has been definite decrease in the leftsided enlargement of the cardiac silhouette since Sept. 22, 1937. Fluoroscopically, pulsations appeared forceful and of normal rate and rhythm. Aorta slender. The infiltrative lesion at the right base has entirely disappeared, only some coarsening of bronchovascular detail remaining in this region. The opacity throughout the left lung has also disappeared. Several strandlike densities remain at the left base, with slight obliteration of the costophrenic sulcus. These have the appearance of old adhesions. Lung fields are now otherwise essentially clear.

TABLE II

SUMMARY OF TREATMENT

DATE	BLOOD TRANSFUSIONS (CITRATED BLOOD)	STOCK STAPHYLOCOCCUS BACTERIOPHAGE	SULFANILAMIDE	STAPHYLOCOCCUS ANTITOXIN
9/15/37	400 c.c.—(chill)	1 c.c. intravenously	40 grains by mouth	
9/14/37	? amount given	1 c.c. intravenously	80 grains by mouth	
9/15/37		1 c.c. intravenously	60 grains by mouth	
9/16/37			60 grains by mouth	
9/17/37			60 grains by mouth	
9/24/37	350 c.c.		60 grains by mouth	
9/25/37	200 c.c.			
10/ 1/37	200 c.c.			5,000 units intramuscularly
10/ 2/37				20,000 units intravenously—(chill)
10/ 4/37				15,000 units intravenously—(chill)
10/ 5/37				20,000 units intravenously—(chill)
10/ 6/37				30,000 units intravenously—(chill)
10/18/37	200 c.c.			
10/20/37	250 c.c.			
10/22/37	150 c.c.			Small amount (? amount)
10/25/37				20,000 units intravenously—(chill)
10/26/37				20,000 units intravenously—(chill)
10/27/37				40,000 units intravenously—(chill and urticaria)
10/28/37				20,000 units intravenously
10/29/37				20,000 units intravenously
10/30/37				20,000 units intravenously
11/10/37	250 c.c.			
11/11/37	200 c.c.—(chill)			
11/19/37	350 c.c.			
12/ 1/37	Part of transfusion with severe reaction			
2/ 4/38				20,000 units intravenously, with cevitamic acid, in divided doses after careful desaritization—(urticaria)
2/ 5/37				10,000 units intravenously with cevitamic acid—(severe reaction)
2/ 6/38				10,000 units intravenously with cevitamic acid—(urticaria, joint effusion, laryngeal edema, precordial pain)
2/ 7/38	300 c.c.—severe reaction			

In the third period, from Jan. 21, 1938, to Feb. 8, 1938, there were two periods of fever: a mild one on January 21, and a severe one starting on February 3, with a chill and temperature of 104° F. At this time, a third course of staphylococcus antitoxin was given, with severe reaction (chills, urticaria, joint effusions, and laryngeal edema), despite careful desensitization.

After the last elevation of temperature, on Feb. 8, 1938, the patient slowly improved, although there were questionable petechiae on March 30, and a questionably positive blood culture in May, 1938. She was discharged from the hospital July 6, 1938, ten and one-half months after entry. At this time she had been up for one month in a wheel chair, with occasional walks around the ward. Her weight was 125 pounds. On entry her weight was 130 pounds, with a low point, four months after entry, of 100 pounds (January, 1938).

She was followed in the outpatient clinic for three months after discharge from the hospital, and showed gain in weight and strength. Because she left Los Angeles, frequent examinations were impossible. However, the patient has kept us informed by letter, about every six months, as to her condition, and has returned to the hospital for examination about once a year. In April, 1941, the cardiac murmur and thrill were unchanged. The last report by letter, December, 1941, states that she is leading an entirely normal life and has no cardiac symptoms.

DISCUSSION

Libman,[1, 2] Hamman,[3] Weiss and Rhoads,[4] and others have commented on the occurrence of healed bacterial endocarditis (of the *Streptococcus viridans* group), clinically and pathologically. It is their experience that, in mild cases, the disease frequently goes undiagnosed, and the patient may recover, and that, in severe cases, the patient may recover and have a later recurrence. Some of the clinical reports of recovery appear doubtful because of possible diagnostic errors and too short periods of observation. The chronicity of the disease requires a period of observation of one and one-half to three years before one can be sure that recovery has occurred. The problem in treatment of typical subacute bacterial endocarditis caused by the *Streptococcus viridans*, however, appears quite distinct and different from the situation encountered in this patient.

No previous reports of recovery from subacute bacterial endocarditis caused by the *Staphylococcus aureus*, with or without treatment with staphylococcus antitoxin, have been found in the literature. The case presented here fulfills the majority of the points for diagnosis of subacute bacterial endocarditis and for recovery from this condition:

1. Known heart lesion seven years prior to the onset of the febrile illness.
2. Positive blood cultures for six months.
3. Evidence of embolic phenomena: petechiae and pulmonary infarcts.
4. Irregular, prolonged febrile illness.
5. Progressive, mild anemia.

Recovery was attested by: (1) negative blood cultures, (2) clinical improvement, and (3) observation for four years.

From the clinical aspect, several features of this case are of interest. No point of origin or entry of the staphylococcus was discovered.

Since small skin lesions may go unnoticed, this does not appear an unlikely possibility. The urine examination on entry excluded the kidneys as a possible focus. It is also of note that the spleen was never palpable, although repeated examinations of the abdomen were made. The finger nails developed very unusual, marked, transverse striations, corresponding chronologically to each separate febrile period.

From the therapeutic standpoint, the relationship of the staphylococcus antitoxin to the recovery is difficult to evaluate. It is a matter of experience that certain patients with acute staphylococcus septicemia recover, but this is rarer with chronic staphylococcus sepsis. Staphylococcus antitoxin was given to this patient because of the dramatic results obtained, at the same time, in a 14-year-old Mexican boy. This patient entered the hospital in an apparently moribund state, with staphylococcus sepsis, with pyemic abscesses in the skin, lungs, and kidneys, and with osteomyelitis. He was given 80,000 units of staphylococcus antitoxin (Lederle) daily for several weeks, with marked improvement within twenty-four hours, and final recovery. It was never possible to give the patient with the endocarditis the antitoxin in the recommended therapeutic dose because of severe reactions. Thus, she received only 90,000 units between October 1 and 6, 140,000 units between October 25 and 30, and 40,000 units between February 3 and 6. From the graphs of the temperature (Fig. 1), it is apparent that the first course of staphylococcus antitoxin was given at a time when the temperature curve was already falling, so that the effect on the temperature is not clear. The improvement in the clinical condition was definite, however. The second course of staphylococcus antitoxin was also given at a time when the temperature was normal. It is to be noted that, after stopping the antitoxin, in each of those instances, the temperature rose. The third and last course of staphylococcus antitoxin was followed by a marked and permanent lowering of the temperature to normal and by negative blood cultures. The severe reactions with practically every injection of antitoxin, as well as with many of the blood transfusions, may also have had a therapeutic effect through a "shock" action. Although no one who saw this patient felt positive about the effect of the staphylococcus antitoxin, the consensus was that it had been beneficial, for the outlook before its use had appeared hopeless. The work of Tager[5] on the relative value of staphylococcus antitoxin and the sulfonamide compounds in acute staphylococcus infections in mice is of interest in this connection. He reviews experimental and clinical results. From his own results he concludes that "a single early dose of antitoxin proved superior to sulfapyridine and sulfathiazole, but did not surpass the activity of sulfamethylthiazole." He believes a combination of antitoxin and sulfathiazole is superior to either agent alone. This he attributes to the possibility that the staphylococcus toxin is an important factor in the pathogenicity of the staphylococcus. The chemotherapeutic agents appear

not to be antitoxic. This work suggests that the best therapeutic results in staphylococcal sepsis would be attained by a combination of the antitoxin and one of the sulfonamide drugs.

SUMMARY

A case of subacute bacterial endocarditis caused by the *Staphylococcus aureus*, with recovery and a four-year period of observation, is reported. The possible beneficial effect of staphylococcus antitoxin in the treatment in this case is discussed.

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RARE CARDIAC ANEURYSM IN A CHILD

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J. HAMILTON CRAWFORD, M.D.
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THE final analysis of the unusual cardiac configuration found in a 13-year-old child, as previously reported in the AMERICAN HEART JOURNAL by Hollander and Crawford,[1] may now be presented with the aid of necropsy observations.

Since the recognition, in 1938, of this cardiac deformity in the child, she was followed in the cardiac clinic, but there was no apparent change in her physical condition. She was last seen in the clinic about six months before her death. Her mother states that the child had been well and active during this time. While at play in one of the city playgrounds, the child became ill and sat down to rest. She died within a short time, before any medical aid could be obtained.

POST-MORTEM EXAMINATION

Because of the sudden death, the post-mortem examination was performed by the Medical Examiner.* It revealed a well-nourished and well-developed, muscular child, measuring 155 cm. in length. There were no external evidences of injury. The essential abnormalities were limited to the heart. The pericardial sac contained a small quantity of clear, straw-colored fluid, and the serosal surfaces were everywhere smooth and glistening. No congenital abnormalities were found in the great vessels. A large, somewhat lobulated, saccular mass bulged from the lateral margin of the left ventricle (Fig. 1). It was completely covered by the visceral pericardium. A few firm, fibrous adhesions bound the superior surface of the aneurysmal sac to the parietal pericardium. Several fibrous adhesions traversed the shallow sulci formed by the superior and inferior lobules of the sac. The aneurysm measured 9 cm. between the superior and inferior surfaces, 6 cm. from the base of the mitral ring to the outermost border, and 6.5 cm. between the anterior and posterior borders of the sac. A sagittal section of the aneurysm (Fig. 2) revealed a lobulated, thin-walled sac in which there were partially formed ridges tending to divide the chamber into two or three incompletely formed compartments. The superior compartment contained a massive, laminated blood clot which was firmly adherent to the inner wall of the sac. The remaining compartments of the aneurysm were free from blood clots. The lining of the sac was smooth, white, and glistening. The thickness of the wall varied from 0.1 to 0.5 mm.; it consisted of white, glistening, connective tissue. The origin of the aneurysm was sharply limited to the fibrous connective tissue ring of the mitral valve, and did not involve the muscular wall of the left ventricle except for the posterior portion, which appeared fused by newly formed connective tissue and by the adipose tissue of the epicardium to the wall of the sac. The orifice of the sac was situated beneath the lateral leaflet of the mitral valve and was in direct communication with the chamber of the left ventricle. The greatest diameter of the opening measured 1.5 cm. A smooth, white, glistening, endocardial surface lined the wall of the orifice. The valve leaflet and

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the cordae tendineae overlying the opening into the sac were not involved. The aneurysm did not distort the architecture of the heart, although the appendage of the left auricle was situated in a pocket formed by the superior pole of the sac and the base of the aorta and pulmonary artery. The heart valves were thin and delicate and showed no gross evidence of either active or healed rheumatic endocarditis. The chorade tendineae were thin and delicate and attached beyond

Fig. 1.

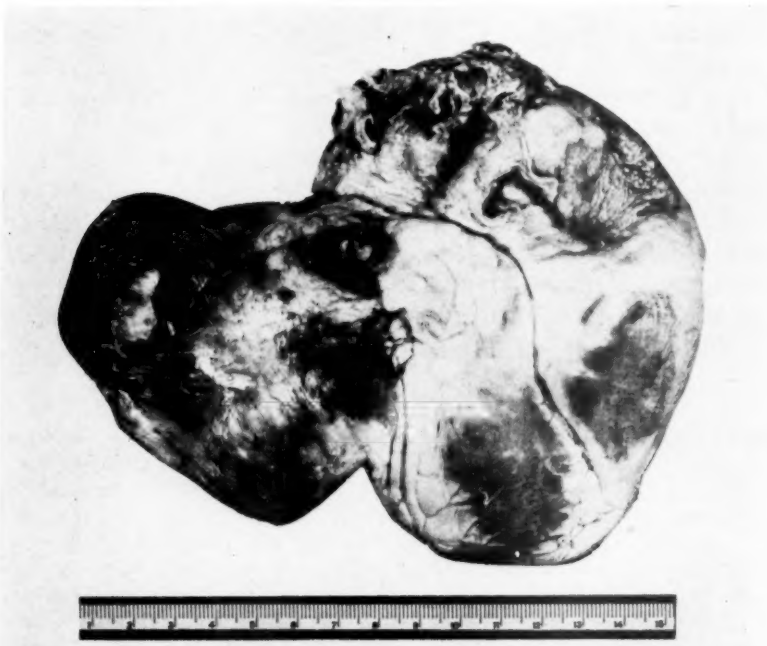

Fig. 2.

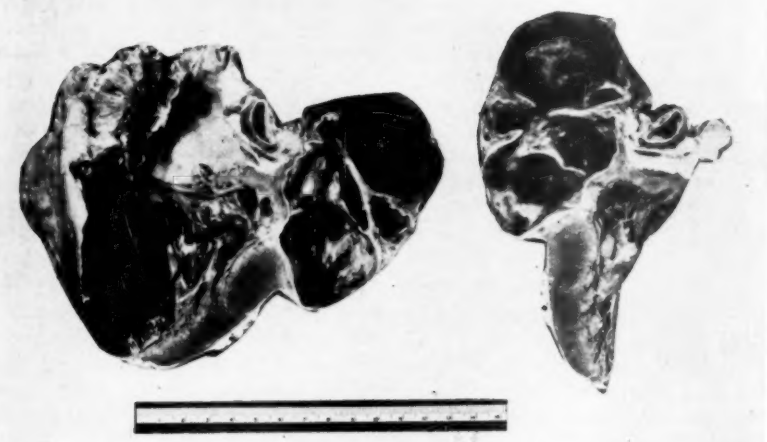

Fig. 1.—Posterior view of heart, with aneurysm arising from left ventricle.

Fig. 2.—Sagittal section of aneurysm, showing opening into left ventricle beneath the lateral leaflet of mitral valve.

the free edge of the valve leaflets. Sections of the myocardium were homogeneous, dull red, and without gross evidence of increased fibrosis. The heart was not hypertrophied nor dilated, but it weighed, together with the aneurysm, 550 grams. The coronary vessels were of the usual distribution. The outer surface of the aneurysm was partially supplied by small branches from the left coronary artery. The coronary vessels were thin walled and patent throughout.

Examination of the other viscera, including the brain, showed no significant changes except acute congestion of the spleen, liver, and lungs.

MICROSCOPIC EXAMINATION

Microscopic sections from a number of different locations of the aneurysmal wall revealed a compact, hyalinized, fibrous, connective tissue wall that was free from endothelial lining. Some of the sections contained either partially organized blood clots or firm, dense masses of fibrin and platelets. The outer wall of the aneurysm consisted of loosely arranged, collagen forming, connective tissue in which there were groups of young, splindle-shaped fibroblasts. Many greatly engorged and thick-walled arterioles were distributed throughout the external coat of the sac. Many of the vessels were surrounded by collars of cells composed primarily of large mononuclear cells, plasma cells, and lymphocytes. An occasional polymorphonuclear leucocyte and eosinophilic cell was observed in the cellular exudate. Some of these foci, particularly those situated near blood vessels, showed a tendency to form imperfectly shaped Aschoff bodies. The mononuclear cells found in these zones were large cells with basophilic cytoplasm containing one and occasionally two large vesicular nuclei which had a central dense clump of chromatin. The exudate not only surrounded the blood vessels, but was rather diffusely scattered throughout the edematous connective tissue in the areolar tissue surrounding the sac. Similar isolated groups of engorged blood vessels, with their collars of mononuclear and plasma cells, were seen in the dense, hyalinized connective tissue wall of the aneurysm. Isolated groups of newly formed lymphoid follicles were observed in some of the sections that were removed from near the base of the sac. Microscopic sections from the ring of the mitral valve, near the region of the orifice of the aneurysm, displayed a granulomatous and cellular tissue reaction that contained many young capillaries, fibroblasts, and an abundant, diffuse, cellular exudate characterized chiefly by large mononuclear cells, plasma cells, and lymphocytes. This granulomatous lesion apparently diffusely involved the entire mitral ring, and in some places extended for a short distance along the interstitial tissue of the mitral leaflet, but did not involve the endocardial surface. Throughout the myocardium of both the left and right ventricles there were many well-developed, typical Aschoff bodies comprised of the usual large mononuclear and binucleated cells, together with some plasma cells and lymphocytes. Some of the muscle fibers appeared small and atrophic. Many focal areas of myocardial fibrosis were observed in all of the sections of the myocardium. The coronary arteries and pericardial surfaces were free from involvement.

COMMENT

An intensive search of the literature revealed only three other reports of a cardiac aneurysm identical in anatomic structure with the one observed in this child. Hunter and Benson[2] described a ruptured saccular aneurysm in a 45-year-old adult who died suddenly. These same authors referred to the only other report in the literature that described a similar cardiac deformity. Corvisart,[3] in 1797, described an aneurysm in a 27-year-old negro who also died suddenly, but without rupture of the sac. More recently Berlin and Hollén[4] described a similar type of

aneurysm in a 39-year-old man. Aneurysms of the heart in children are extremely uncommon, as mentioned in the previous report.[1]

Certain outstanding anatomic characteristics, common to all three of the aneurysms described, seem to distinguish these unusual cardiac deformities from the better known cardiac aneurysms which result from coronary occlusion. In each of the cases reported, the out-pouching developed on the lateral border of the left ventricle, and seemed to arise chiefly from the fibrous ring of the mitral valve. The opening into the aneurysm is small and is located inferior to the lateral leaflet of the valve. There is some tendency to lobulation of the sac and to development of incompletely formed chambers from poorly formed septa. No muscle fibers are present in the wall of the sac except for a few isolated strands that fuse into the base of the aneurysm from the left ventricle.

Unfortunately, a detailed history of the earlier period of the child's life is not available, so that the time of onset and progress of the development of this aneurysm are not known. Several of the anatomic features of the aneurysm suggest that it may have been a congenital development from the fibrous band of the mitral ring. On the other hand, the presence of both acute and chronic rheumatic lesions in the interstitial tissue points to an inflammatory reaction as a possible etiological factor. Certainly, coronary occlusion and syphilitic inflammatory reactions are eliminated as factors in the formation of this saccular aneurysm.

SUMMARY

The necropsy observations on an unusual and rare cardiac aneurysm in a child are reported. The anatomic characteristics of the structure suggest that it was a congenital abnormality arising from the fibrous band of the mitral ring.

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Correspondence

To the Editor:

In the paper by Wood, Wolferth, and Geckeler, entitled "Histologic Demonstration of Accessory Muscular Connections between Auricle and Ventricle in a Case of Short P-R Interval and Prolonged QRS Complex," published in the AMERICAN HEART JOURNAL, April, 1943, p. 454, there appears parenthetically the categorical statement: "Kent was the first to describe the auriculoventricular bundle, although His' name has been applied to it," which I feel should not be permitted to pass unchallenged.

I have prepared a fully documented analysis of the relevant literature, but it is entirely too long for publication as "Correspondence." What follows is a brief summary of the cardinal points made in the full account, which I am attaching to this letter.

In 1892-1893, Kent searched for muscular tissue bridging the A-V junction in subhuman hearts. In one and the same heart he claims to have found it crossing the ring in various localities in the form of "nets," "bands," and "sheets." Yet he concluded this series of papers with the statement: "In a later paper I propose to deal with the exact location of the connection between auricles and ventricles. . . ." The illustrations consist of seven reproductions of histologic preparations. One is from the "junction of right auricle and ventricle;" the part of the junction supplying the other sections is not specified. In none can features characteristic of the A-V bundle be recognized.

In 1894, relative to the human heart, he speaks of "strands" of muscular tissue passing across the groove in unspecified locations, and, in addition, describes a mass muscular continuity, not at all resembling the A-V bundle, but in a situation which might have included the septum, although, if this mass contact included, or was in, the septum, that is not mentioned.

In a series of papers published during 1913-1914, Kent, without in the meanwhile having dealt "with the exact location of the connection," (1) states he has maintained since 1892 that "the muscular path of communication is undoubtedly multiple;" (2) deals specifically with "a muscular connection . . . at the right margin of the heart," which he says he "described in 1892 in lower animals and in 1893 in man" (I have not succeeded in finding specific mention of a connection in that location in the only paper by Kent [1894] that deals with the human heart); and (3) states that after severing "all of the structures which connect the auricles to the ventricles with the exception of a strip of

tissue on the right lateral aspect of the organ, spontaneous beats arising in the auricle still pass through to the ventricle and evoke ventricular beats,'' a result which, I say advisedly, never has been confirmed by any investigator.

Certainly no one could have surmised, on the basis of the above exhibit, that there is a particular muscular connection in the septal region of the A-V junction, or that functional integrity of a path there, is essential to the maintenance of the normal A-V sequence.

Now for the chronology of *the* A-V bundle. It is exactly identified, both descriptively and pictorially, in a number of mammals including man, by His, in a paper appearing in ''Arbeiten aus der medizinischen Klinik zu Leipzig,'' the preface to which, dated March, 1893, states that the volume consists of ''an account of research conducted during the last four years. . . .''

In 1895, His announced that section of only this one bundle produces lasting heart block, a result since abundantly confirmed; and, in 1899, he described the first case of heart block to be recognized in man. Here His thus summarizes correctly the situation relative to the question of muscular continuity across the layer of connective tissue in the A-V junction: ''Muscle fibers,'' he says, ''have been found in this layer (Kent) and I myself have demonstrated a bundle which is present both in mammals and in man, and runs from the posterior wall of the right auricle to the ventricular septum.''

In conclusion, may I add that if, as Kent maintains, there is a right lateral muscular connection in all mammals (in addition to the many other connections he claims he has seen), it is obvious that it does not function as a path for A-V conduction under experimental conditions, Kent to the contrary notwithstanding. And if it is such a right lateral connection that is responsible for the rare clinical condition described by Wood, et al., one ponders the nature of the process that converts a connection which cannot, by experimental procedures, be made to conduct vicariously, into one which transmits impulses faster than the normal path. Is it not possible that short P-R intervals may be the result of a physiologic anomaly rather than an anatomic anomaly?

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Abstracts and Reviews

Selected Abstracts

Bond, D. D.: Sympathetic and Vagal Interaction in Emotional Responses of the Heart Rate. Am. J. Physiol. **138**: 468, 1943.

Changes in heart rate of unanesthetized dogs and cats, startled by a short, unexpected noise, were recorded electrically. The cardiac responses from the animals when normal were compared to the responses from the same animals after various nerves had been cut.

Intact dogs and cats yielded a complex pattern of a sudden, high rise in heart rate, beginning immediately after the startle. This was successively followed by a sharp fall, more pronounced in dogs, a second rise of variable height, and, thereafter, several undulations in rate until a termination of the response in two to three minutes.

Adrenaline plays a more prominent role in cats than in dogs; but its action in either species appears only after twelve seconds.

Dogs in which the vagi and depressors were cut and adrenaline excluded showed pure accelerator activity. The response was similar to that of the normal in promptness and magnitude, but was simpler, with no secondary fall or further undulations.

In dogs and cats with the sympathetic cardio-accelerators removed, and with adrenaline excluded, startle was promptly followed by inhibition of vagal tone. Cats, in addition, showed an acceleration that was greater than could be accounted for by loss of vagal tonic influence alone. Unless there were a few rapid beats of vagal origin occurring in certain individuals immediately after the stimulus, no fall in rate subsequent to the initial rise was seen. If these rapid beats were present, they were commonly followed by one very slow beat only. This seems to indicate that usually the increase of heart rate did not raise arterial pressure to a degree sufficient to trip a depressor mechanism acting primarily through the vagus. Evidence is presented that the carotid sinus is involved.

The effect of respiration on cardiac rhythm is complex and may greatly affect the pattern of response. Apnea may cause a speeding of the heart or may be accompanied by a slowing.

The discussion deals with the quick activity of the sympathetics, the role of the vagus, and the relation of the responses reported here to those obtained by others from direct and reflex cardiac acceleration.

AUTHOR.

Hitchings, G. H., Daus, M. A., and Wearn, J. T.: Chemical Changes in the Rabbit Heart During Hypertrophy. Am. J. Physiol. **138**: 527, 1943.

When aortic insufficiency is produced in the rabbit heart by rupturing an aortic valve leaflet, rapid changes occur in the chemical composition of the myocardium. During the first three days there is a transient increase of extracellular phase of considerable magnitude. The intracellular phase appears to hypertrophy at a more or less constant rate for several weeks, after which further increases cannot be clearly distinguished. The hypertrophied hearts at intermediate periods are characterized by a proportion of intracellular phase somewhat greater than normal, but of approximately normal composition, except for an increased intracellular water content. At later periods, a tendency for a loss of intracellular constituents is observed.

AUTHORS.

Rosenblueth, A., and Acheson, G. H.: The Influence of Interelectrodal Distance in Electrical Stimulation of Nerve and of Striated and Ventricular Muscle. Am. J. Physiol. **138:** 583, 1943.

With short distances between the stimulating electrodes, the threshold of C nerve fibers rises significantly, but not as much as does that of A fibers.

The threshold of striated and ventricular muscle to electrical stimuli is independent of the interelectrodal distance. The threshold of striated muscle is also independent of the angle between the stimulating current and the muscle fibers.

AUTHORS.

Neumann, C.: A Study of the Effect of Spontaneous Variations in Blood Pressure Upon Spontaneous Variations in the Volume of the Finger Tip. Am. J. Physiol. **138:** 618, 1943.

By the simultaneous use of a plethysmograph for recording changes in volume of the tip of the left index finger, and of an intra-arterial manometer for obtaining synchronous readings of the blood pressure of the left radial artery, it was shown that the spontaneous variations (increase or decrease) in volume of the finger tip are not concordant with spontaneous changes in blood pressure (? Traube-Hering waves), and are present even in the absence of measurable variations in blood pressure. A few exceptions were noticed. Rises in systemic blood pressure during expiration were accompanied by variable but small increases in volume of the finger tip. Marked lowering of blood pressure accompanying cardiac asystole was reflected in a decrease in volume. The rule then seems to be that variations in the volume of the finger tip usually go on independent of changes, or lack of change, in blood pressure, though under certain conditions there may be a transitory relationship. When present, it is manifested by an increase in volume when there is a rise in blood pressure.

AUTHOR.

Lewis, T.: Trosseau's Phenomenon in Tetany. Clin. Sc. **4:** 361, 1942.

In a case of tetany, Trosseau's sign was easily elicited. It has been shown, in this case, that the spasmodic affection of the hand, on occluding the circulation to the arm, resulted from ischemia of the nerves under the cuff. The phenomena of irritation described by Trosseau, and those of paralysis where the nerves of the normal limb are deprived of circulation, are interestingly comparable, though the former are naturally much earlier manifestations.

AUTHOR.

Lewis, T.: Observations Upon the Vascular Axon Reflex in Human Skin, As Exhibited by a Case of Urticaria, With Remarks Upon the Nocifensor Nerve Hypothesis. Clin. Sc. **4:** 365, 1942.

A case of urticaria, with occasional subcutaneous swellings, is described, in which a general skin eruption could be produced by applying heat to the lower limbs.

In addition, a constellation of urticarial wheals could be produced at, and around, the site of a quite local cutaneous stimulus, such as heat, freezing, severe pressure, or faradism; it could be reproduced around histamine punctures of the skin.

The constellation of wheals fell always within the area exhibiting the vascular flare, and, when sufficiently extensive, corresponded closely with the distribution of the latter.

As in the case of the flare, so this reaction was found to be dependent upon the functional integrity of cutaneous nerves, but to be independent of the central nervous

system. Flare and satellite wheal are regarded as produced through the same nervous mechanism, an axon reflex.

Because general whealing of this patient's skin could be induced by injecting pilocarpine subcutaneously, and local whealing, by ionizing either pilocarpine or an acetylcholine compound into the skin, and because the spontaneous eruption could be controlled by atropine, the nerves involved are regarded as cholinergic.

The occurrence of satellite wheals in the area of flare is evidence of H-substance release through the axon reflex. Such a release links the axon reflex effects with antidromic vasodilatation. In view of the work of Grant, Pearson, and Comeau, and of the present observations, both these effects are now regarded as produced by one and the same system of cholinergic nerves.

The abnormal factor in the patient was in the skin itself, this organ being rendered unusually responsive by some abnormal quality of the patient's blood plasma.

Between two hypotheses, that which supposes antidromic impulses and axon reflexes to make use of sensory (pain) nerve channels, and that which supposes them to make use of special (nocifensor) nerve channels belonging to the posterior root system, the balance of evidence appears still to favor the latter.

AUTHOR.

Cohen, H., and Jones, H. W.: The Reference of Cardiac Pain to a Phantom Left Arm. Brit. Heart J. **5**: 67, 1943.

Two cases are recorded of cardiac pain referred to a phantom left arm.

Anesthetization of the brachial plexus of the phantom caused, in one case, abolition of the phantom component of the cardiac pain, and in the other, significant delay in the appearance of the phantom component, which led to a reversal of the site of onset and spread of cardiac pain.

AUTHORS.

Horvath, S. M., Dill, D. B., and Corwin, W.: Effects on Man of Severe Oxygen Lack. Am. J. Physiol. **138**: 659, 1943.

Schizophrenic patients have been subjected to severe anoxia over a period of several minutes either up to the point of unconsciousness or in some cases extending into unconsciousness. The following conclusions are drawn:

Anoxia of severe degree produces no beneficial effects on the mental condition of this class of psychotic patients.

Anoxia severe enough to produce brief periods of unconsciousness has no lasting harmful effects on the central nervous system.

Respiratory stimulation by anoxia is strong and sustained even during unconsciousness.

Inferentially, circulatory function is also well sustained.

There is a remarkably rapid return to normal when either air or 14 per cent oxygen is supplied.

A mixture of 4.2 per cent oxygen with nitrogen is equivalent physiologically to an altitude of about 31,000 feet.

It should be possible to descend with an opened parachute from 31,000 feet altitude, without oxygen equipment, with no ill effects from anoxia.

AUTHORS.

Cossio, P., Berconsky, I., and Trimani, A.: The Formation of Auricular Diastolic Murmurs in Complete A-V Heart Block. Rev. argent. de cardiol. **9**: 238, 1942.

The recording of the heart sounds in three cases of complete auriculoventricular block showed that the auricular sound was formed by two components of vibrations.

The first component was more marked at the beginning of the ventricular diastole, disappearing sometimes when auricular systole occurred at the end of the ventricular diastole. The second component did not change in intensity throughout diastole, or was more marked when it occurred toward the end of auricular systole.

These findings support the hypothesis that the vibrations of the first component of the auricular sound are due to distention of the ventricle, while those of the second component are due to elevation and tension of the auriculoventricular valves, once terminating auricular systole.

AUTHORS.

Bozler, E.: The Initiation of Impulses in Cardiac Muscle. Am. J. Physiol. 138: 273, 1943.

The action potentials of isolated cardiac muscle were recorded in an attempt to detect the processes which initiate the beats and which are responsible for the rhythmicity of heart action. Confirming earlier work on other muscles with automaticity, it was found that spontaneous impulses are initiated by weak local potentials, which are present in a large part of the muscular tissue, but which are strongest near the origin of the impulses. A phase of gradually rising negativity precedes each impulse in muscles with normal rhythmicity, but in injured muscles, there may be instead regular potential oscillations of gradually increasing magnitude. These oscillations give rise to the phenomenon of the Luciani periods if several waves in succession cause the discharge of impulses.

Each impulse is followed by an afterpotential which is normally positive, but which is oscillatory under certain abnormal conditions. The oscillations of the afterpotential may give rise to the discharge of further impulses like those of prepotentials. Acetylcholine diminishes the magnitude of the oscillations in the auricle and sinus venosus, but not in the ventricle; adrenaline increases their magnitude. None of the drugs alter their frequency.

It may be expected that a consideration of the local potentials will be helpful in the understanding of certain types of abnormal rhythmicity of the heart.

AUTHOR.

Hoff, H. E., Nahum, L. H., and Kaufman, W.: Distribution in Leads I, II, and III of Potentials Applied to the Surface of the Heart. Am. J. Physiol. 138: 644, 1943.

Potential differences applied across the surfaces of the right and left ventricles cause an upward deflection in the standard leads of the electrocardiogram when the negative electrode is on the right ventricle, and a downward deflection when the negative plate is on the left ventricle.

Potential differences applied across the centers of the anterior surface of the right ventricle and the posterior surface of the left ventricle affect preponderantly Lead III of the electrocardiogram. The projection in the horizontal plane of the line joining these centers is roughly parallel to the longitudinal axis of the body.

Potential differences applied across the centers of the anterior surface of the left ventricle and the posterior surface of the right ventricle are recorded preponderantly in Lead I. The projection in the horizontal plane of the line joining these centers is roughly parallel to the transverse axis of the body.

AUTHORS.

Langendorf, R., Hurwitz, M., and Katz, L. N.: Electrocardiographic Patterns of Combined Ventricular Strain. Brit. Heart J. 5: 27, 1943.

An analysis of forty-seven cases showing a combination of features of right and left ventricular strain in the cardiogram is presented. These were then cor-

related with clinical data and, in nineteen instances, with the available autopsy findings.

Six electrocardiographic patterns of combined ventricular strain are described.

The cardiographic diagnosis of combined ventricular strain was substantiated by clinical, radiologic, or post-mortem evidence in 81 per cent of the cases.

In a control group of twenty-nine autopsied cases of bilateral ventricular hypertrophy, in the absence of myocardial infarction, acute cor pulmonale, intraventricular block, or digitalis effect in the cardiogram, cardiographic evidence of combined strain was present in 27.5 per cent. In 35 per cent of the same series, no ventricular preponderance and no axis deviation, or only normal right or left axis shift, were present; this substantiates the statement that absence of ventricular preponderance in the cardiogram, in the presence of clinical or radiologic evidence of cardiac enlargement, is presumptive evidence of combined ventricular strain.

Other factors like displacement of the heart, congenital anomaly of the conduction system, or focal intraventricular block may be responsible for a pattern suggestive of combined ventricular strain.

Further anatomical correlation studies are necessary to establish the diagnostic accuracy of the cardiographic patterns of combined ventricular strain.

AUTHORS.

Williams, C., and Ellis, L. B.: Ventricular Tachycardia: An Analysis of Thirty-Six Cases. Arch. Int. Med. **71**: 137, 1943.

An analysis is reported of thirty-six cases of paroxysmal ventricular tachycardia. In twenty-four, the electrocardiograms showed the attack to be uninterrupted, and in twelve the attacks occurred in short runs of tachycardia interposed between periods of normal supraventricular conduction. These two types have been arbitrarily designated as "persistent" and "intermittent" tachycardia.

In all but one case, organic heart disease was present; in twenty-eight cases it was of the degenerative type.

Digitalis intoxication was clearly associated with the attack in eight instances and was the probable precipitating factor in nine more. One patient had received large doses of both digitalis and quinidine prior to the onset of the attack. Attacks occurred in association with myocardial infarction six times, and in three instances, myocardial infarction was probably present.

Twenty-one patients died in the hospital, eight in the attack, and twelve (all but one of the remainder) within a month of its cessation.

The occurrence and prognosis of the attacks have also been analyzed in respect to associated electrocardiographic abnormalities and such factors as age, heart rate, and width of QRS. The prognosis of paroxysmal ventricular tachycardia is serious, but it is essentially the prognosis of the underlying heart disease present. In our series, the prognosis of the "intermittent" type was somewhat better than that of the "persistent" type.

The physiologic mechanism involved, the clinical symptomatology, the criteria for the clinical and electrocardiographic diagnosis, and the therapy of the attacks with particular reference to quinidine are discussed.

AUTHORS.

Peel, A. A. F.: Congenital Heart Block With Atrial and Ventricular Septal Defect. Brit. Heart J. **5**: 11, 1943.

A case of atrial septal defect with ventricular septal defect and congenital complete heart block is described and discussed. The patient had fairly good health until she was 40 years of age, and was still working as a housekeeper at 46 years of age.

AUTHOR.

Campbell, M.: Congenital Complete Heart Block. Brit. Heart J. 5: 15, 1943.

The present condition of seven patients with congenital complete heart block, now aged 42, 36, 31, 28, 26, 25, and 22 years is reported. Full details about six of the cases were published nine years ago. All six and one other (first seen shortly after the paper was published) have been traced, a very satisfactory result after this interval of nine years, especially in war time.

All are alive and well, and their degree of activity could be taken as a fair cross section of the general public. Of the four men, two are working men, who, though rejected from the army, have led strenuous lives, both in their work and in their play, almost certainly doing more than they ought to as their hearts are not normal. One has been two years in the R.A.F. and has been passed for flying duties, and the fourth is a professional man who leads a normal life, with gardening and cycling in his spare time.

Of the three women the eldest does ordinary housework on a farm, but the other two lead rather more sheltered lives, possibly because their doctors discouraged them. One was at easy work till she developed tuberculosis a year before her marriage, and the other, after doing light duties at home for six years, has taken up sedentary work since the war. Except for the one case of tuberculosis, no unexpected developments have arisen in any case, and the one who had Stokes-Adams attacks in infancy has led the most strenuous life, with only two short periods of recurrences.

Congenital complete heart block is not rare. It is overlooked because the rate is relatively fast, about 40 to 56, and also because the possibility is not remembered.

If there are no special complications carrying special risks of their own, the prognosis is good, and it will probably prove that the condition is compatible with survival to old age.

AUTHOR.

Touroff, A. S. W.: Blood Cultures From Pulmonary Artery and Aorta in Patient With Infected Patent Ductus Arteriosus. Proc. Soc. Exper. Biol. & Med. 49: 568, 1942.

Blood was taken and cultured directly from the aorta and pulmonary artery during an operation for subacute bacterial endarteritis superimposed on patent ductus arteriosus. The results demonstrated that the lungs removed infective material from the circulating blood of human beings and that, in the type of case under consideration, infective material enters the peripheral circulation, at least in part, through the pulmonary circuit.

KERSHBAUM.

Roosen, R.: The Role of Human Microdiencephalus in the Pathogenesis of Degenerative Heart Disease. Cardiologia 6: 214, 1942.

The degenerative heart and vessel diseases are not primary, independent changes but conditions following human microdiencephalus.

AUTHOR.

Bramwell, C.: Signs Simulating Those of Mitral Stenosis. Brit. Heart J. 5: 24, 1943.

In a consecutive series of 835 recruits, a duplicated second heart sound (generally associated with an apical systolic murmur) was present in 157 cases.

The duplicated second heart sound was best heard when the patient lay on his left side; the reason for this is discussed. Duplication of the second heart sound

was much more common in men under 20 years of age than in older recruits. Seventy per cent of the men in whom it was present were considered fit for Grade I. Radioscopy in these cases generally showed an increased prominence of the pulmonary arc.

Since the production of an obstructive murmur depends on the degree of obstruction relative to the velocity of the blood current, it is suggested that an increased rate of blood flow through a normal mitral orifice may be instrumental in producing: (a) the accentuation and roughening of the first heart sound heard in certain athletes, in thyrotoxicosis, and in other conditions in which the heart is overacting, and (b) the duplicated second heart sound heard in healthy subjects. Both these signs are therefore regarded as signifying a "relative" mitral stenosis.

This hypothesis entails a physiologic conception of mitral stenosis based on the volume of blood which an orifice of a certain size can transmit in unit time.

AUTHOR.

Jager, B. V., and Ransmeier, J. C.: Constrictive Pericarditis Due to Bacterium Tularense. Report of a Case and Review of Reported Cases of Pericarditis Occurring With Tularemia. Bull. Johns Hopkins Hosp. **72**: 166, 1943.

The authors have presented a case of tularemia of the typhoidal type with evidence of pleuritis and pneumonia. The illness was complicated by a constricting pericarditis which persisted after clinical recovery from the febrile illness. Roentgenograms following instillation of air into the pericardial sac showed the pericardium to be markedly thickened. *B. tularense* was recovered from the pleural fluid of this patient. In addition there was suggestive evidence that this organism was present in the pericardial fluid. The manifestations of nine additional cases of pericardial involvement in tularemia are tabulated and discussed.

AUTHORS.

Ditkowsky, S. P., Stevenson, E., and Campbell, J. M.: An Epidemic of Rheumatic Fever in a Children's Institution Following an Outbreak of Acute Tonsillitis. J. A. M. A. **121**: 991, 1943.

An epidemic of rheumatic fever in a children's school followed an outbreak of acute tonsillitis. Two hundred forty-one children had acute hemolytic infections of the throat, and eighty-eight children in the institution showed manifestations of rheumatic fever. The conclusion reached after studying various features of the epidemic are:

The epidemiology of rheumatic fever is closely linked with that of streptococcic infections of the upper respiratory tract.

Familial prediposition on the basis of specific tissue susceptibility probably is an important factor in the pathogenesis of rheumatic fever.

The most susceptible age group appeared to be between 9 and 14 years. Sex did not appear to be a factor.

Sixty-two children (65 per cent) had histories compatible with previous rheumatic infections. Sixty-one children had systolic apical murmurs elicited before the present rheumatic attack, most of them having the characteristics ascribed to functional murmurs. This would suggest that the murmurs should be observed repeatedly before they are dismissed as insignificant.

No direct correlation could be made between meteorologic conditions and the incidence of rheumatic fever. It was felt that they were important so far as they were related to the seasonal incidence of infections of the upper respiratory tract.

AUTHORS.

Fox, T. T., and Kremer, H. S.: The Heart in Pulmonary Tuberculosis: Studies of the Auricular Complex in the Electrocardiogram. Am. Rev. Tuberc. 47: 135, 1943.

Electrocardiographic tracings of 804 patients with pulmonary tuberculosis were analyzed, with particular reference to the occurrence of abnormal auricular complexes.

Sixty-nine tracings were found to possess abnormal P waves; thirty-eight tracings in this group had notching and spiking in Leads II and III; sixteen out of the thirty-eight tracings were associated with clinical and roentgenological evidence of bilateral tuberculosis and emphysema.

Fifteen cases of severe emphysema were studied electrocardiographically. Eight cases had a low P_1, and a notched and spiked P_2 and P_3.

Fifteen cases with post-mortem evidence of right ventricular hypertrophy, without hypertrophy of the left ventricle, showed findings not fully confirmatory of the observations stated above. The predominant electrocardiographic abnormality in this group was an abnormal P_2.

To study the effect of change in position on the auricular complex, ten cases with changes in the P wave of Lead I had electrocardiograms taken in the supine, left lateral, and right lateral positions. Only six cases had directional changes in the QRS complex. All cases showed changes in the configuration of the P wave with change of position of the patient.

In order to see the effect of transient overfilling of the right auricle on the electrocardiogram, ten patients in congestive failure, with enlarged livers and prominent jugular veins, had tracings taken prior to, and after, pressure upon the liver sufficient to increase the volume of the jugular veins to a marked extent. No change took place in shape or amplitude of the previously normal P waves in the eight cases with sinus rhythm.

It is the authors' impression that P-wave changes cannot serve as a criterion for the existence of cor pulmonale in cases of pulmonary tuberculosis (or other gross pulmonary disease) where such information is most desirable. On the other hand, P-wave changes are frequently the sole electrocardiographic evidence of mediastinal displacement.

In the course of this study two additional interesting observations were made:

In a limited number of cases studied, inversion of the P_1 was almost universally associated with displacement due to right pneumothorax.

Changes in the measurable P-R interval in the electrocardiogram of cases with pulmonary tuberculosis may be due to mediastinal displacement or distortion. These changes are probably expressions of structural divergences of the P waves, and are not indicative of altered A-V conduction or shift in the pacemaker.

AUTHORS.

Fitz, R., Walker, B. S., and Branch, C. F.: Polycythaemia Vera: Report of a Case. Arch. Int. Med. 70: 919, 1942.

The case described appears unusual in that it is the first example of the disease to be described in which the clinical picture of polycythemia vera was seen to develop in a person previously regarded as normal, and in which its clinical earmarks disappeared under treatment, leaving behind a variety of interesting vestiges of its previous existence. The blood count had returned to normal in every way, and had remained normal for the rest of the patient's life. He died suddenly four and one-half years after his course of roentgen treatment had been completed. Examination of vertebral and sternal bone marrow, and of the spleen showed a degree of hematopoietic activity not ordinarily encountered in a person with chronic heart

failure. The individual died with a general vascular lesion which may have been related to the polycythemia. The authors discuss various phases of the situation and the possible causes of polycythemia.

McCULLOCH.

Grollman, A., and Rule, C.: Experimentally Induced Hypertension in Parabiotic Rats. Am. J. Physiol. **138**: 587, 1943.

Rats were joined in parabiotic union and their systolic blood pressures determined daily, following operative procedures on the kidney. Parabiotic individuals retain an independence of their circulatory adjustments; hypertensive blood pressure levels may be maintained in one member of a parabiotic pair, while the blood pressure of the co-twin remains normal. In some instances, however, the hypertensive action induced by procedures on the kidney is transmitted to the intact co-twin. The results are interpreted as being most consistent with the view that the kidney normally elaborates a substance necessary for the maintenance of normal blood pressure levels. The bearing of the results on other current theories of the pathogenesis of experimental renal hypertension is discussed.

AUTHORS.

Abell, R. G., and Page, I. H.: The Effects of Renal Hypertension on the Vessels of the Ears of Rabbits. J. Exper. Med. **75**: 673, 1942.

Experimental renal hypertension in rabbits causes persistent, visible constriction to occur in the arterioles of the ears which is not great enough to restrict the flow of blood to the tissues but is sufficient to increase peripheral resistance. The constriction is due to the direct action of a substance on the arterioles since it occurs in the absence of nerves to vessels. It is associated with the appearance of new arteriovenous anastomoses. Since many of these phenomena have been reproduced by injection of angiotonin, this evidence is consonant with the view that the hypertension is due to angiotonin or some similar substance.

AUTHORS.

Eichelberger, L.: The Distribution of Water and Electrolytes Between Blood and Skeletal Muscle in Experimental Hypertension. J. Exper. Med. **77**: 205, 1943.

The effect of an abnormal renal circulation and a resulting hypertension on the distribution of water and electrolytes in skeletal muscle of dogs was as follows: By analysis of the muscle the total content of sodium and chloride was found increased, and the total potassium content decreased. A redistribution of water occurred in the muscle, involving a shift of water from the muscle cells to the extracellular phase (F) = 254, plus-minus 54 Gm., intracellular water $(H_2O)_c$ = 532, plus-minus 47 Gm., and total solids (S) = 214, plus-minus 8 Gm. This extracellular phase volume of 254 Gm. represents an increase of 65 per cent over that found in normal dog muscle.

After subjecting the hypertensive dogs to large increases in total body water produced by the intravenous injection of normal isotonic salt solution, the total bulk of 1 kilogram of muscle increased a mean average of 103 Gm., of which one-half was attributed to the extracellular phase and one-half to the swelling of the muscle cells.

Whether the changes found in this study are the result of the functional disturbances caused by the experimental renal abnormalities, or the hypertension, or a combination of both is uncertain at this time. The significance of the results is that there is quantitative evidence that a redistribution of water has occurred in skeletal muscle so that a real extracellular edema exists.

AUTHOR.

Wiggers, C. J., Wégria, R., and Nickerson, N. D.: Reactions of the Aorta in Hemorrhagic Hypotension and Shock. Am. J. Physiol. 138: 491, 1943.

On the basis of negative evidence from three modes of experimental approach, the authors conclude that it appears highly improbable that active changes in the aortic wall play any role in the initiation or progression of hemorrhagic shock or in the establishment of an irreversible state.

AUTHORS.

Page, I. H., and Abell, R. G.: The State of the Vessels of the Mesentery in Shock Produced by Constricting the Limbs and the Behavior of the Vessels Following Hemorrhage. J. Exper. Med. 77: 215, 1943.

Direct observations of the arteries, arterioles, capillaries, veins, and lymphatics in the mesentery of anesthetized cats put into shock by incomplete occlusion of the circulation showed that:

Marked constriction of the arteries and arterioles, produced by muscular contraction, occurred usually within an hour after incomplete occlusion of the limbs, lasted several hours, and finally gave way in most instances to relaxation an hour or more before death. The constriction reduced the blood supply to the mesentery and intestine, and the venous return from them. It did not, however, interrupt the blood flow. No pooling or stagnation of blood was seen even as a terminal phenomenon.

The veins of the mesentery also became constricted, but showed less tendency to dilate as death approached. The lymphatics likewise became somewhat narrowed. Even during the terminal stage the leucocytes moved along without change in shape and without sticking to the walls of the capillaries or venules.

Hematocrit determinations showed progressive hemoconcentration of moderate degree.

Autopsy usually showed the presence of small hemorrhages in many parts of the body, especially the heart, liver, spleen, and lungs.

Bilateral nephrectomy, suprarenalectomy, and pancreatectomy did not significantly alter the morphologic picture elicited by shock induced by restriction of the circulation to the limbs.

Removal of large amounts of blood was always followed within a short time by constriction of arteries, arterioles, veins, and lymphatics of the mesentery.

Fall in arterial pressure produced by pithing was not accompanied by change in diameter of the arteries, arterioles, veins, or lymphatics, or by blanching of the mesentery or gut.

AUTHORS.

Rich, A. R., and Gregory, J. E.: The Experimental Demonstration That Periarteritis Nodosa Is a Manifestation of Hypersensitivity. Bull. Johns Hopkins Hosp. 72: 65, 1943.

Typical diffuse periarteritis nodosa has been produced experimentally by establishing in rabbits a condition analogous to serum sickness in man.

These experiments demonstrate that periarteritis nodosa is one manifestation of the anaphylactic type of hypersensitivity.

The clinical and pathologic evidence, presented in previous papers, shows that periarteritis nodosa has developed in patients as a result of hypersensitive reactions following foreign serum and sulfonamide therapy. This is supported by the present experiments, and shows that widely different types of sensitizing antigens are capable of causing periarteritis nodosa in man, and suggests the advisability of attempting to discover and to eliminate the responsible antigen in each case diagnosed clinically.

The continued administration of foreign serum or sulfonamides after a hypersensitive reaction has occurred, or the injection of a single large amount of foreign

serum, increases the danger of producing the vascular damage by prolonging the contact of the sensitized body with the offending antigen.

Acute diffuse glomerulonephritis occurred in a number of the animals that developed a hypersensitive reaction to the foreign serum. This supports the view that some cases of glomerulonephritis in man may be due to hypersensitivity.

AUTHORS.

Steiner, A., and Domanski, B.: Serum Cholesterol Level in Coronary Arteriosclerosis. Arch. Int. Med. **71**: 397, 1943.

The serum cholesterol level in patients with coronary arteriosclerosis is significantly higher than the serum cholesterol level in normal subjects.

The serum cholesterol level in patients with coronary arteriosclerosis is inconstant and fluctuates widely.

The claim of relative constancy of the serum cholesterol level in normal persons is further substantiated.

AUTHORS.

Loutit, J. F., Mollison, M. D., van der Walt, E. D.: Venous Pressure During Venesection and Blood Transfusion. Brit. M. J. 2: 658, 1942.

The venesection of normal subjects is accompanied by a fall in venous pressure. During the following thirty minutes there is a return toward the original venous pressure, although this level is not regained in this period.

During the transfusion of blood to unselected hospital patients there is, in the majority of cases, a rise of venous pressure which is approximately proportional to the amount given and occurs more frequently at the faster rates. Signs and symptoms suggestive of peripheral vasodilatation were encountered in three of the forty-three cases transfused. In these cases vasodilatation occurred after a rise in venous pressure and was not followed by a fall.

After transfusion, patients suffering from pulmonary disease showed signs of pulmonary congestion, as revealed by a reduction in vital capacity. This decrease was not related to the venous pressure changes.

AUTHORS.

Abramson, D. I., Flachs, K., Freiberg, J., and Mirsky, I. A.: Blood Flow in Extremities Affected by Anterior Poliomyelitis. Arch. Int. Med. **71**: 391, 1943.

The rate of blood flow during rest was measured by the venous occlusion plethysmographic method in a series of twenty-seven subjects with acute or chronic anterior poliomyelitis of one extremity.

It was found that in the majority of cases the peripheral circulation in the paralyzed limb was the same as that in the contralateral normal extremity; in fact, in some instances it was significantly greater.

Evidence was obtained which indicated that the cutaneous blood vessels in the extremity affected by anterior poliomyelitis respond more markedly to the stimulus of cold than do those of the contralateral normal limb. The response takes the form of excessive vasoconstriction on exposure to a low environmental temperature, and is apparent as a significant decrease in cutaneous temperature.

By studying the changes in blood flow during the reactive hyperemia elicited by a period of arterial occlusion, some evidence was obtained which suggested that the metabolism of muscles atrophied by poliomyelitis is the same as that of normal tissues.

In view of the lack of evidence for the hypothesis that the peripheral circulation is reduced in persons with anterior poliomyelitis, it is concluded that those treatments which have for an aim the increase in blood flow through the affected parts should be critically re-examined for their therapeutic value.

AUTHORS.

Bordley, J., III, Gladston, M., and Dandy, W. E.: The Treatment of Essential Hypertension by Sympathectomy. A Report on Twelve Patients Three to Seven Years Following Operation. Bull. Johns Hopkins Hosp. **72**: 127, 1943.

The presence of incapacitating symptoms was the only criterion for sympathectomy in twelve patients with essential hypertension.

The level of arterial pressure was lowered for six to eighteen months in four of the nine patients treated by the infradiaphragmatic operation (Adson-Craig), and for four and one-half years in one of the three patients treated by the supradiaphragmatic operation (Peet).

Symptomatic relief appeared to depend upon lowered arterial pressure in four of nine patients in whom it occurred.

In two patients abnormal findings in the heart and eye grounds regressed during the period of lowered arterial pressure and returned after the arterial pressure rose again.

Return of arterial pressure to preoperative hypertensive levels was not associated with regeneration of the sympathetic nerves supplying the lower extremities, which were severed during the Adson-Craig operation.

AUTHORS.

Chen, K. K., Hargreaves, C. C., and Robbins, E. B.: Comparison of Digoxin, Digilanids A, B, and C, and Deacetyldigilanids A and B. J. Am. Pharm. A. **31**: 236, 1942.

Six glycosides of *Digitalis lanata:* digoxin, digilanids A, B, and C, and deacetyldigilanids A and B, have been assayed in cats and frogs. In cats, the order of activity from high to low is: digoxin and digilanid C, digilanids A and B, deacetyldigilanid A, deacetyldigilanid B. The results in frogs do not follow those in cats. The order of potency from high to low is: digilanid A, deacetyldigilanid A, digoxin, deacetyldigilanid B, digilanids B and C. The differences of the last three compounds are apparently not significant.

AUTHORS.

Chen, K. K., and Elderfield, R. C.: Synthetic Derivatives of Strophanthidin. J. Pharmacol. & Exper. Therap. **76**: 81, 1942.

Strophanthidin acetate and seven synthetic glycosides of strophanthidin all have a digitalis-like action.

When assayed in cats and frogs, strophanthidin acetate, strophanthidin-β-*d*-glucoside, -*d*-xyloside, and -*l*-arabinoside, prove more potent than strophanthidin. Strophanthidin-β-tetraacetyl-*d*-glucoside, -triacetyl-*d*-xyloside, -triacetyl-*l*-arabinoside, and -tetraacetyl-*d*-galactoside, on the other hand, are weaker than strophanthidin.

Strophanthidin-β-*d*-glucoside and -*l*-arabinoside are also more potent than cymarin, the natural glycoside from which strophanthidin is originally obtained. Strophanthidin-β-*d*-xyloside is at least as active as cymarin.

AUTHORS.

Book Review

CLINICAL ROENTGENOLOGY OF THE CARDIOVASCULAR SYSTEM: By Hugo Roesler, M.D., F.A.C.P., Associate Professor of Roentgenology and Cardiologist, Department of Medicine, Temple University School of Medicine; Cardiologist, Temple University Hospital, Philadelphia. Second edition. Charles C Thomas, Springfield, Ill., 1943, 480 pages, 337 illustrations, $7.50.

The second edition of this authoritative volume has made its position as the classic work in the field of cardiovascular roentgenology fully secure. Housed in a handsome binding, printed with great clarity, adorned with numerous and unusually well reproduced illustrations, the physical characteristics are in keeping with the nature of the contents, and both arouse enthusiasm on the part of the reviewer. Certainly no cardiologist, no internist, no roentgenologist can afford to be without this book.

The entire work has been revised; greater detail has been added to most of the chapters, and almost all the newest studies on roentgenologic examination of the heart have been included. The addition of about 135 pages of text, a similar number of new figures, and the inclusion of well over 2,500 references make the new edition most complete. The bibliography is particularly excellent; only a few of the important references of the past two years have been omitted. The increased material on roentgen technique is especially valuable. The author has also added a considerable amount of detail on contrast cardiography, on cardiac measurements, and on the secondary changes in the lungs incident to cardiac failure.

Obviously, there are some statements with which issue can be taken. For example, the conclusion that patency of the ductus arteriosus occurs more frequently in association with other congenital defects than as a solitary process is not in accord with the experience of investigators who have studied this problem in connection with the surgical treatment. It may apply to stillborns and young infants. The author's detailed description of the roentgenologic characteristics of patency of the ductus arteriosus, however, is most timely, and represents a conservative and well-grounded estimation of the value of x-ray examination. On the whole, there is very little with which to disagree and very much to commend. The work is thorough, painstaking, sound, and well presented. The second edition of this book is a tribute to the publishers, and particularly to the author, whose authority in this field is unquestionable.

LEO G. RIGLER.

American Heart Association, Inc.

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THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The AMERICAN HEART JOURNAL is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the AMERICAN HEART JOURNAL (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

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